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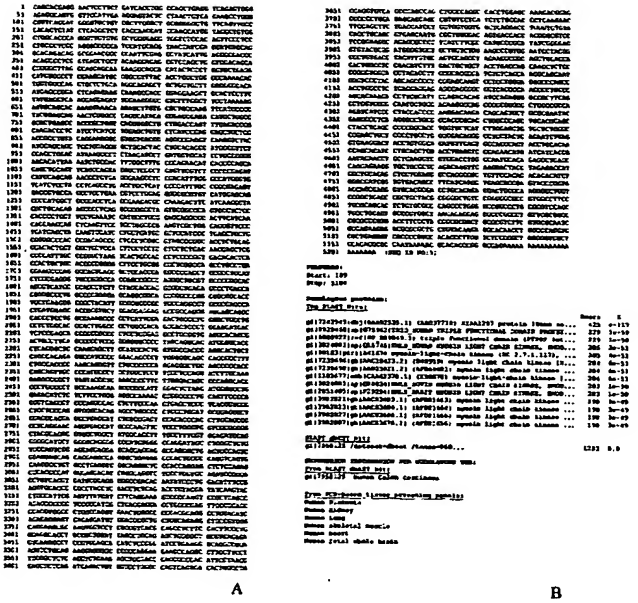

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(57) Abstract: The present invention provides amino acid sequences of peptides that are encoded by genes within the human genome, the kinase peptides of the present invention. The present invention specifically provides isolated peptide and nucleic acid molecules, methods of identifying orthologs and paralogs of the transporter peptides, and methods of identifying modulators of the kinase peptides.

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ISOLATED HUMAN KINASE PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN KINASE PROTEINS, AND USES THEREOF

RELATED APPLICATIONS

The present application is a Continuation-In-Part of US Serial No. 09/711,134, filed November 14, 2000 (Atty. Docket CL000927), and U.S. Serial No. 09/858,664 filed May 17, 2001(Atty. Docket CL000927-CIP).

FIELD OF THE INVENTION

The present invention is in the field of kinase proteins that are related to the myosin light chain kinase subfamily, recombinant DNA molecules, and protein production. The present invention specifically provides novel peptides and proteins that effect protein phosphorylation and nucleic acid molecules encoding such peptide and protein molecules, all of which are useful in the development of human therapeutics and diagnostic compositions and methods.

BACKGROUND OF THE INVENTION

Protein Kinases

Kinases regulate many different cell proliferation, differentiation, and signaling processes by adding phosphate groups to proteins. Uncontrolled signaling has been implicated in a variety of disease conditions including inflammation, cancer, arteriosclerosis, and psoriasis. Reversible protein phosphorylation is the main strategy for controlling activities of eukaryotic cells. It is estimated that more than 1000 of the 10,000 proteins active in a typical mammalian cell are phosphorylated. The high energy phosphate, which drives activation, is generally transferred from adenosine triphosphate molecules (ATP) to a particular protein by protein kinases and removed from that protein by protein phosphatases. Phosphorylation occurs in response to extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc), cell cycle checkpoints, and environmental or nutritional stresses and is roughly analogous to turning on a molecular switch. When the switch goes on, the appropriate protein kinase activates a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor.

The kinases comprise the largest known protein group, a superfamily of enzymes with widely varied functions and specificities. They are usually named after their substrate, their

regulatory molecules, or some aspect of a mutant phenotype. With regard to substrates, the protein kinases may be roughly divided into two groups; those that phosphorylate tyrosine residues (protein tyrosine kinases, PTK) and those that phosphorylate serine or threonine residues (serine/threonine kinases, STK). A few protein kinases have dual specificity and phosphorylate threonine and tyrosine residues. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The N-terminal domain, which contains subdomains I-IV, generally folds into a two-lobed structure, which binds and orients the ATP (or GTP) donor molecule. The larger C terminal lobe, which contains subdomains VI A-XI, binds the protein substrate and carries out the transfer of the gamma phosphate from ATP to the hydroxyl group of a serine, threonine, or tyrosine residue. Subdomain V spans the two lobes.

The kinases may be categorized into families by the different amino acid sequences (generally between 5 and 100 residues) located on either side of, or inserted into loops of, the kinase domain. These added amino acid sequences allow the regulation of each kinase as it recognizes and interacts with its target protein. The primary structure of the kinase domains is conserved and can be further subdivided into 11 subdomains. Each of the 11 subdomains contains specific residues and motifs or patterns of amino acids that are characteristic of that subdomain and are highly conserved (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Books*, Vol I:7-20 Academic Press, San Diego, Calif.).

The second messenger dependent protein kinases primarily mediate the effects of second messengers such as cyclic AMP (cAMP), cyclic GMP, inositol triphosphate, phosphatidylinositol, 3,4,5-triphosphate, cyclic-ADPribose, arachidonic acid, diacylglycerol and calcium-calmodulin. The cyclic-AMP dependent protein kinases (PKA) are important members of the STK family. Cyclic-AMP is an intracellular mediator of hormone action in all prokaryotic and animal cells that have been studied. Such hormone-induced cellular responses include thyroid hormone secretion, cortisol secretion, progesterone secretion, glycogen breakdown, bone resorption, and regulation of heart rate and force of heart muscle contraction. PKA is found in all animal cells and is thought to account for the effects of cyclic-AMP in most of these cells. Altered PKA expression is implicated in a variety of disorders and diseases including cancer, thyroid disorders, diabetes, atherosclerosis, and cardiovascular disease (Isselbacher, K. J. *et al.* (1994) *Harrison's Principles of Internal Medicine*, McGraw-Hill, New York, N.Y., pp. 416-431, 1887).

Calcium-calmodulin (CaM) dependent protein kinases are also members of STK family. Calmodulin is a calcium receptor that mediates many calcium regulated processes by binding to

target proteins in response to the binding of calcium. The principle target protein in these processes is CaM dependent protein kinases. CaM-kinases are involved in regulation of smooth muscle contraction (MLC kinase), glycogen breakdown (phosphorylase kinase), and neurotransmission (CaM kinase I and CaM kinase II). CaM kinase I phosphorylates a variety of substrates including the neurotransmitter related proteins synapsin I and II, the gene transcription regulator, CREB, and the cystic fibrosis conductance regulator protein, CFTR (Haribabu, B. *et al.* (1995) *EMBO Journal 14*:3679-86). CaM II kinase also phosphorylates synapsin at different sites, and controls the synthesis of catecholamines in the brain through phosphorylation and activation of tyrosine hydroxylase. Many of the CaM kinases are activated by phosphorylation in addition to binding to CaM. The kinase may autophosphorylate itself, or be phosphorylated by another kinase as part of a "kinase cascade".

Another ligand-activated protein kinase is 5'-AMP-activated protein kinase (AMPK) (Gao, G. *et al.* (1996) *J. Biol Chem. 15*:8675-81). Mammalian AMPK is a regulator of fatty acid and sterol synthesis through phosphorylation of the enzymes acetyl-CoA carboxylase and hydroxymethylglutaryl-CoA reductase and mediates responses of these pathways to cellular stresses such as heat shock and depletion of glucose and ATP. AMPK is a heterotrimeric complex comprised of a catalytic alpha subunit and two non-catalytic beta and gamma subunits that are believed to regulate the activity of the alpha subunit. Subunits of AMPK have a much wider distribution in non-lipogenic tissues such as brain, heart, spleen, and lung than expected. This distribution suggests that its role may extend beyond regulation of lipid metabolism alone.

The mitogen-activated protein kinases (MAP) are also members of the STK family. MAP kinases also regulate intracellular signaling pathways. They mediate signal transduction from the cell surface to the nucleus via phosphorylation cascades. Several subgroups have been identified, and each manifests different substrate specificities and responds to distinct extracellular stimuli (Egan, S. E. and Weinberg, R. A. (1993) *Nature 365*:781-783). MAP kinase signaling pathways are present in mammalian cells as well as in yeast. The extracellular stimuli that activate mammalian pathways include epidermal growth factor (EGF), ultraviolet light, hyperosmolar medium, heat shock, endotoxic lipopolysaccharide (LPS), and pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1).

PRK (proliferation-related kinase) is a serum/cytokine inducible STK that is involved in regulation of the cell cycle and cell proliferation in human megakaroytic cells (Li, B. *et al.* (1996) *J. Biol. Chem. 271*:19402-8). PRK is related to the polo (derived from humans polo gene) family of STKs implicated in cell division. PRK is downregulated in lung tumor tissue and may

be a proto-oncogene whose deregulated expression in normal tissue leads to oncogenic transformation. Altered MAP kinase expression is implicated in a variety of disease conditions including cancer, inflammation, immune disorders, and disorders affecting growth and development.

The cyclin-dependent protein kinases (CDKs) are another group of STKs that control the progression of cells through the cell cycle. Cyclins are small regulatory proteins that act by binding to and activating CDKs that then trigger various phases of the cell cycle by phosphorylating and activating selected proteins involved in the mitotic process. CDKs are unique in that they require multiple inputs to become activated. In addition to the binding of cyclin, CDK activation requires the phosphorylation of a specific threonine residue and the dephosphorylation of a specific tyrosine residue.

Protein tyrosine kinases, PTKs, specifically phosphorylate tyrosine residues on their target proteins and may be divided into transmembrane, receptor PTKs and nontransmembrane, non-receptor PTKs. Transmembrane protein-tyrosine kinases are receptors for most growth factors. Binding of growth factor to the receptor activates the transfer of a phosphate group from ATP to selected tyrosine side chains of the receptor and other specific proteins. Growth factors (GF) associated with receptor PTKs include; epidermal GF, platelet-derived GF, fibroblast GF, hepatocyte GF, insulin and insulin-like GFs, nerve GF, vascular endothelial GF, and macrophage colony stimulating factor.

Non-receptor PTKs lack transmembrane regions and, instead, form complexes with the intracellular regions of cell surface receptors. Such receptors that function through non-receptor PTKs include those for cytokines, hormones (growth hormone and prolactin) and antigen-specific receptors on T and B lymphocytes.

Many of these PTKs were first identified as the products of mutant oncogenes in cancer cells where their activation was no longer subject to normal cellular controls. In fact, about one third of the known oncogenes encode PTKs, and it is well known that cellular transformation (oncogenesis) is often accompanied by increased tyrosine phosphorylation activity (Carbonneau H and Tonks NK (1992) *Annu. Rev. Cell. Biol. 8*:463-93). Regulation of PTK activity may therefore be an important strategy in controlling some types of cancer.

Myosin Light Chain Kinase

Activation of smooth/nonmuscle myosin light chain kinase (MLCK) by Ca/calmodulin results in phosphorylation of myosin regulatory light chain that plays important roles in initiation of smooth muscle contraction, endothelial cell retraction, secretion, and other cellular processes

(Stull et al., in *International Symposium on Regulation of the Contractile Cycle in Smooth Muscle, April 26, 1995, Mie, Japan*). The same myosin light chain kinases are present in smooth and nonmuscle tissues.(Gallagher et al., *J Biol Chem* 1991 Dec 15;266(35):23936-44, Published erratum appears in *J Biol Chem* 1992 May 5;267(13):9450). The phosphorylation of myosin light chains by myosin light chain kinase is a key event in agonist-mediated endothelial cell gap formation and vascular permeability. Amino acid sequence analysis indicates endothelial MLCK consensus sequences for a variety of protein kinases including highly conserved potential phosphorylation sites for cAMP-dependent protein kinase A (PKA) in the CaM-binding region. Augmentation of intracellular cAMP levels markedly enhanced MLCK phosphorylation (2.5-fold increase) and reduced kinase activity in MLCK immunoprecipitates (4-fold decreases) (Garcia et al., *Am J Respir Cell Mol Biol* 1997 May;16(5):489-94). The smooth/nonmuscle myosin light chain kinase contains a catalytic core homologous to that of other protein kinases and a carboxyl-terminal regulatory domain consisting of both an inhibitory sequence and a calmodulin-binding sequence (Kemp et al., *Trends Biochem. Sci.* 19, 440-444, 1994; Stull et al., 1995). Initially, inspection of the linear sequence within the regulatory domain revealed a similar number and sequential arrangement of 4 basic residues with those shown to be important substrate determinants in a synthetic peptide containing residues 11-23 of the myosin regulatory light chain . Thus, it has been proposed that the regulatory domain contained a pseudosubstrate inhibitory sequence whereby 4 specific basic residues in myosin light chain kinase mimic the basic substrate determinants in the light chain peptide substrate . Binding of the pseudosubstrate sequence to the active site inhibited activity. Intrasteric inhibition involves an autoinhibitory sequence that folds back on the catalytic site to inhibit kinase activity as opposed to an allosteric mechanism whereby a conformational change induced at a site distinct from the active site would be responsible for regulation of enzyme activity (Kemp et al., *Biochim. Biophys. Acta.* 1094, 67-76, 1991). The sequence comprising the pseudosubstrate region was later expanded to include overlap with the complete amino terminus of the light chain (Faux et al., *Mol. Cell. Biochem.* 128, 81-91, 1993). However, these additional residues(1, 2, 3, 4, 5, 6, 7, 8, 9, 10) are not important for substrate binding and thus are not part of the consensus phosphorylation sequence (Kemp et al., *Trends Biochem. Sci.* 15, 342-346, 1990).

Kinase proteins, particularly members of the myosin light chain kinase subfamily, are a major target for drug action and development. Accordingly, it is valuable to the field of pharmaceutical development to identify and characterize previously unknown members of this subfamily of kinase proteins. The present invention advances the state of the art by providing

previously unidentified human kinase proteins that have homology to members of the myosin light chain kinase subfamily.

SUMMARY OF THE INVENTION

The present invention is based in part on the identification of amino acid sequences of human kinase peptides and proteins that are related to the myosin light chain kinase subfamily, as well as allelic variants and other mammalian orthologs thereof. These unique peptide sequences, and nucleic acid sequences that encode these peptides, can be used as models for the development of human therapeutic targets, aid in the identification of therapeutic proteins, and serve as targets for the development of human therapeutic agents that modulate kinase activity in cells and tissues that express the kinase. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma.

DESCRIPTION OF THE FIGURE SHEETS

FIGURE 1 provides the nucleotide sequence of a cDNA molecule or transcript sequence that encodes the kinase protein of the present invention. (SEQ ID NO:1) In addition, structure and functional information is provided, such as ATG start, stop and tissue distribution, where available, that allows one to readily determine specific uses of inventions based on this molecular sequence. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma.

FIGURE 2 provides the predicted amino acid sequence of the kinase of the present invention. (SEQ ID NO:2) In addition structure and functional information such as protein family, function, and modification sites is provided where available, allowing one to readily determine specific uses of inventions based on this molecular sequence.

FIGURE 3 provides genomic sequences that span the gene encoding the kinase protein of the present invention. (SEQ ID NO:3) In addition structure and functional information, such as intron/exon structure, promoter location, etc., is provided where available, allowing one to readily determine specific uses of inventions based on this molecular sequence. 6 SNPs, have been identified in the gene encoding the kinase protein provided by the present invention and are given in Figure 3.

DETAILED DESCRIPTION OF THE INVENTION

General Description

The present invention is based on the sequencing of the human genome. During the sequencing and assembly of the human genome, analysis of the sequence information revealed previously unidentified fragments of the human genome that encode peptides that share structural and/or sequence homology to protein/peptide/domains identified and characterized within the art as being a kinase protein or part of a kinase protein and are related to the myosin light chain kinase subfamily. Utilizing these sequences, additional genomic sequences were assembled and transcript and/or cDNA sequences were isolated and characterized. Based on this analysis, the present invention provides amino acid sequences of human kinase peptides and proteins that are related to the myosin light chain kinase subfamily, nucleic acid sequences in the form of transcript sequences, cDNA sequences and/or genomic sequences that encode these kinase peptides and proteins, nucleic acid variation (allelic information), tissue distribution of expression, and information about the closest art known protein/peptide/domain that has structural or sequence homology to the kinase of the present invention.

In addition to being previously unknown, the peptides that are provided in the present invention are selected based on their ability to be used for the development of commercially important products and services. Specifically, the present peptides are selected based on homology and/or structural relatedness to known kinase proteins of the myosin light chain kinase subfamily and the expression pattern observed. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. The art has clearly established the commercial importance of members of this family of proteins and proteins that have expression patterns similar to that of the present gene. Some of the more specific features of the peptides of the present invention, and the uses thereof, are described herein, particularly in the Background of the Invention and in the annotation provided in the Figures, and/or are known within the art for each of the known myosin light chain kinase family or subfamily of kinase proteins.

Specific Embodiments

Peptide Molecules

The present invention provides nucleic acid sequences that encode protein molecules that have been identified as being members of the kinase family of proteins and are related to the

myosin light chain kinase subfamily (protein sequences are provided in Figure 2, transcript/cDNA sequences are provided in Figure 1 and genomic sequences are provided in Figure 3). The peptide sequences provided in Figure 2, as well as the obvious variants described herein, particularly allelic variants as identified herein and using the information in Figure 3, will be referred herein as the kinase peptides of the present invention, kinase peptides, or peptides/proteins of the present invention.

The present invention provides isolated peptide and protein molecules that consist of, consist essentially of, or comprise the amino acid sequences of the kinase peptides disclosed in the Figure 2, (encoded by the nucleic acid molecule shown in Figure 1, transcript/cDNA or Figure 3, genomic sequence), as well as all obvious variants of these peptides that are within the art to make and use. Some of these variants are described in detail below.

As used herein, a peptide is said to be "isolated" or "purified" when it is substantially free of cellular material or free of chemical precursors or other chemicals. The peptides of the present invention can be purified to homogeneity or other degrees of purity. The level of purification will be based on the intended use. The critical feature is that the preparation allows for the desired function of the peptide, even if in the presence of considerable amounts of other components (the features of an isolated nucleic acid molecule is discussed below).

In some uses, "substantially free of cellular material" includes preparations of the peptide having less than about 30% (by dry weight) other proteins (i.e., contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins. When the peptide is recombinantly produced, it can also be substantially free of culture medium, i.e., culture medium represents less than about 20% of the volume of the protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of the peptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the kinase peptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

The isolated kinase peptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. For example, a

nucleic acid molecule encoding the kinase peptide is cloned into an expression vector, the expression vector introduced into a host cell and the protein expressed in the host cell. The protein can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques. Many of these techniques are described in detail below.

Accordingly, the present invention provides proteins that consist of the amino acid sequences provided in Figure 2 (SEQ ID NO:2), for example, proteins encoded by the transcript/cDNA nucleic acid sequences shown in Figure 1 (SEQ ID NO:1) and the genomic sequences provided in Figure 3 (SEQ ID NO:3). The amino acid sequence of such a protein is provided in Figure 2. A protein consists of an amino acid sequence when the amino acid sequence is the final amino acid sequence of the protein.

The present invention further provides proteins that consist essentially of the amino acid sequences provided in Figure 2 (SEQ ID NO:2), for example, proteins encoded by the transcript/cDNA nucleic acid sequences shown in Figure 1 (SEQ ID NO:1) and the genomic sequences provided in Figure 3 (SEQ ID NO:3). A protein consists essentially of an amino acid sequence when such an amino acid sequence is present with only a few additional amino acid residues, for example from about 1 to about 100 or so additional residues, typically from 1 to about 20 additional residues in the final protein.

The present invention further provides proteins that comprise the amino acid sequences provided in Figure 2 (SEQ ID NO:2), for example, proteins encoded by the transcript/cDNA nucleic acid sequences shown in Figure 1 (SEQ ID NO:1) and the genomic sequences provided in Figure 3 (SEQ ID NO:3). A protein comprises an amino acid sequence when the amino acid sequence is at least part of the final amino acid sequence of the protein. In such a fashion, the protein can be only the peptide or have additional amino acid molecules, such as amino acid residues (contiguous encoded sequence) that are naturally associated with it or heterologous amino acid residues/peptide sequences. Such a protein can have a few additional amino acid residues or can comprise several hundred or more additional amino acids. The preferred classes of proteins that are comprised of the kinase peptides of the present invention are the naturally occurring mature proteins. A brief description of how various types of these proteins can be made/isolated is provided below.

The kinase peptides of the present invention can be attached to heterologous sequences to form chimeric or fusion proteins. Such chimeric and fusion proteins comprise a kinase peptide operatively linked to a heterologous protein having an amino acid sequence not substantially homologous to the kinase peptide. "Operatively linked" indicates that the kinase peptide and the

heterologous protein are fused in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the kinase peptide.

In some uses, the fusion protein does not affect the activity of the kinase peptide *per se*. For example, the fusion protein can include, but is not limited to, enzymatic fusion proteins, for example beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, MYC-tagged, HI-tagged and Ig fusions. Such fusion proteins, particularly poly-His fusions, can facilitate the purification of recombinant kinase peptide. In certain host cells (e.g., mammalian host cells), expression and/or secretion of a protein can be increased by using a heterologous signal sequence.

A chimeric or fusion protein can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different protein sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see Ausubel *et al.*, *Current Protocols in Molecular Biology*, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST protein). A kinase peptide-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the kinase peptide.

As mentioned above, the present invention also provides and enables obvious variants of the amino acid sequence of the proteins of the present invention, such as naturally occurring mature forms of the peptide, allelic/sequence variants of the peptides, non-naturally occurring recombinantly derived variants of the peptides, and orthologs and paralogs of the peptides. Such variants can readily be generated using art-known techniques in the fields of recombinant nucleic acid technology and protein biochemistry. It is understood, however, that variants exclude any amino acid sequences disclosed prior to the invention.

Such variants can readily be identified/made using molecular techniques and the sequence information disclosed herein. Further, such variants can readily be distinguished from other peptides based on sequence and/or structural homology to the kinase peptides of the present invention. The degree of homology/identity present will be based primarily on whether the peptide is a functional variant or non-functional variant, the amount of divergence present in the paralog family and the evolutionary distance between the orthologs.

To determine the percent identity of two amino acid sequences or two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% or more of the length of a reference sequence is aligned for comparison purposes. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity and similarity between two sequences can be accomplished using a mathematical algorithm. (*Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part 1*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (Devereux, J., *et al., Nucleic Acids Res. 12(1)*:387 (1984)) (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Myers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated

into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against sequence databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (*J. Mol. Biol.* 215:403-10 (1990)). BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the proteins of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (*Nucleic Acids Res.* 25(17):3389-3402 (1997)). When utilizing BLAST and gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

Full-length pre-processed forms, as well as mature processed forms, of proteins that comprise one of the peptides of the present invention can readily be identified as having complete sequence identity to one of the kinase peptides of the present invention as well as being encoded by the same genetic locus as the kinase peptide provided herein. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 1 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention encoding a novel phosphatase maps to public BAC AC AC023889, which is known to be located on human chromosome 1.

Allelic variants of a kinase peptide can readily be identified as being a human protein having a high degree (significant) of sequence homology/identity to at least a portion of the kinase peptide as well as being encoded by the same genetic locus as the kinase peptide provided herein. Genetic locus can readily be determined based on the genomic information provided in Figure 3, such as the genomic sequence mapped to the reference human. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 1 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention encoding a novel phosphatase maps to public BAC AC AC023889, which is known to be located on human chromosome 1. As used herein, two proteins (or a region of the proteins) have significant homology when the amino acid sequences are typically at least about 70-80%, 80-90%, and more typically at least about 90-95% or more homologous. A significantly

homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid sequence that will hybridize to a kinase peptide encoding nucleic acid molecule under stringent conditions as more fully described below.

Figure 3 provides information on SNPs that have been identified in a gene encoding the kinase protein of the present invention. 6 SNP variants were found, and all SNPs in exons, of which 3 of these cause changes in the amino acid sequence (i.e., nonsynonymous SNPs). The changes in the amino acid sequence that these SNPs cause is indicated in Figure 3 and can readily be determined using the universal genetic code and the protein sequence provided in Figure 2 as a reference.

Paralogs of a kinase peptide can readily be identified as having some degree of significant sequence homology/identity to at least a portion of the kinase peptide, as being encoded by a gene from humans, and as having similar activity or function. Two proteins will typically be considered paralogs when the amino acid sequences are typically at least about 60% or greater, and more typically at least about 70% or greater homology through a given region or domain. Such paralogs will be encoded by a nucleic acid sequence that will hybridize to a kinase peptide encoding nucleic acid molecule under moderate to stringent conditions as more fully described below.

Orthologs of a kinase peptide can readily be identified as having some degree of significant sequence homology/identity to at least a portion of the kinase peptide as well as being encoded by a gene from another organism. Preferred orthologs will be isolated from mammals, preferably primates, for the development of human therapeutic targets and agents. Such orthologs will be encoded by a nucleic acid sequence that will hybridize to a kinase peptide encoding nucleic acid molecule under moderate to stringent conditions, as more fully described below, depending on the degree of relatedness of the two organisms yielding the proteins.

Non-naturally occurring variants of the kinase peptides of the present invention can readily be generated using recombinant techniques. Such variants include, but are not limited to deletions, additions and substitutions in the amino acid sequence of the kinase peptide. For example, one class of substitutions are conserved amino acid substitution. Such substitutions are those that substitute a given amino acid in a kinase peptide by another amino acid of like characteristics. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr; exchange of the acidic residues Asp and Glu; substitution between the amide residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr. Guidance

concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, *Science 247*:1306-1310 (1990).

Variant kinase peptides can be fully functional or can lack function in one or more activities, e.g. ability to bind substrate, ability to phosphorylate substrate, ability to mediate signaling, etc. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in non-critical regions. Figure 2 provides the result of protein analysis and can be used to identify critical domains/regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree.

Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncation or a substitution, insertion, inversion, or deletion in a critical residue or critical region.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, *Science 244*:1081-1085 (1989)), particularly using the results provided in Figure 2. The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as kinase activity or in assays such as an *in vitro* proliferative activity. Sites that are critical for binding partner/substrate binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol. 224*:899-904 (1992); de Vos *et al. Science 255*:306-312 (1992)).

The present invention further provides fragments of the kinase peptides, in addition to proteins and peptides that comprise and consist of such fragments, particularly those comprising the residues identified in Figure 2. The fragments to which the invention pertains, however, are not to be construed as encompassing fragments that may be disclosed publicly prior to the present invention.

As used herein, a fragment comprises at least 8, 10, 12, 14, 16, or more contiguous amino acid residues from a kinase peptide. Such fragments can be chosen based on the ability to retain one or more of the biological activities of the kinase peptide or could be chosen for the ability to perform a function, e.g. bind a substrate or act as an immunogen. Particularly important fragments are biologically active fragments, peptides that are, for example, about 8 or more amino acids in length. Such fragments will typically comprise a domain or motif of the kinase peptide, e.g., active site, a transmembrane domain or a substrate-binding domain. Further, possible fragments include,

but are not limited to, domain or motif containing fragments, soluble peptide fragments, and fragments containing immunogenic structures. Predicted domains and functional sites are readily identifiable by computer programs well known and readily available to those of skill in the art (e.g., PROSITE analysis). The results of one such analysis are provided in Figure 2.

Polypeptides often contain amino acids other than the 20 amino acids commonly referred to as the 20 naturally occurring amino acids. Further, many amino acids, including the terminal amino acids, may be modified by natural processes, such as processing and other post-translational modifications, or by chemical modification techniques well known in the art. Common modifications that occur naturally in kinase peptides are described in basic texts, detailed monographs, and the research literature, and they are well known to those of skill in the art (some of these features are identified in Figure 2).

Known modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

Such modifications are well known to those of skill in the art and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as *Proteins - Structure and Molecular Properties*, 2nd Ed., T.E. Creighton, W. H. Freeman and Company, New York (1993). Many detailed reviews are available on this subject, such as by Wold, F., *Posttranslational Covalent Modification of Proteins*, B.C. Johnson, Ed., Academic Press, New York 1-12 (1983); Seifter *et al.* (*Meth. Enzymol. 182*: 626-646 (1990)) and Rattan *et al.* (*Ann. N.Y. Acad. Sci. 663*:48-62 (1992)).

Accordingly, the kinase peptides of the present invention also encompass derivatives or analogs in which a substituted amino acid residue is not one encoded by the genetic code, in which a substituent group is included, in which the mature kinase peptide is fused with another compound, such as a compound to increase the half-life of the kinase peptide (for example, polyethylene glycol), or in which the additional amino acids are fused to the mature kinase peptide, such as a

leader or secretory sequence or a sequence for purification of the mature kinase peptide or a pro-protein sequence.

Protein/Peptide Uses

The proteins of the present invention can be used in substantial and specific assays related to the functional information provided in the Figures; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its binding partner or ligand) in biological fluids; and as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state). Where the protein binds or potentially binds to another protein or ligand (such as, for example, in a kinase-effector protein interaction or kinase-ligand interaction), the protein can be used to identify the binding partner/ligand so as to develop a system to identify inhibitors of the binding interaction. Any or all of these uses are capable of being developed into reagent grade or kit format for commercialization as commercial products.

Substantial chemical and structural homology exists between the kinase protein of the present invention described herein and myosin light chain kinase (see Figure 1). As discussed in the background, myosin light chain kinase are known in the art to be involved in smooth muscle contraction, endothelial cell retraction, secretion, and other cellular process. Accordingly, the myosin light chain kinase, and the encoding gene, provided by the present invention is useful for treating, preventing, and/or diagnosing disorders associated with muscle, endothelial cells.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

The potential uses of the peptides of the present invention are based primarily on the source of the protein as well as the class/action of the protein. For example, kinases isolated from humans and their human/mammalian orthologs serve as targets for identifying agents for use in mammalian therapeutic applications, e.g. a human drug, particularly in modulating a biological or pathological response in a cell or tissue that expresses the kinase. Experimental data as provided in Figure 1 indicates that kinase proteins of the present invention are expressed in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma.

Specifically, a virtual northern blot shows expression in human colon carcinoma. In addition, PCR-based tissue screening panel indicates expression in human placenta, kidney, lung, skeletal muscle, heart, and fetal brain. A large percentage of pharmaceutical agents are being developed that modulate the activity of kinase proteins, particularly members of the myosin light chain kinase subfamily (see Background of the Invention). The structural and functional information provided in the Background and Figures provide specific and substantial uses for the molecules of the present invention, particularly in combination with the expression information provided in Figure 1. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Such uses can readily be determined using the information provided herein, that which is known in the art, and routine experimentation.

The proteins of the present invention (including variants and fragments that may have been disclosed prior to the present invention) are useful for biological assays related to kinases that are related to members of the myosin light chain kinase subfamily. Such assays involve any of the known kinase functions or activities or properties useful for diagnosis and treatment of kinase-related conditions that are specific for the subfamily of kinases that the one of the present invention belongs to, particularly in cells and tissues that express the kinase. Experimental data as provided in Figure 1 indicates that kinase proteins of the present invention are expressed in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Specifically, a virtual northern blot shows expression in human colon carcinoma. In addition, PCR-based tissue screening panel indicates expression in human placenta, kidney, lung, skeletal muscle, heart, and fetal brain.

The proteins of the present invention are also useful in drug screening assays, in cell-based or cell-free systems. Cell-based systems can be native, i.e., cells that normally express the kinase, as a biopsy or expanded in cell culture. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. In an alternate embodiment, cell-based assays involve recombinant host cells expressing the kinase protein.

The polypeptides can be used to identify compounds that modulate kinase activity of the protein in its natural state or an altered form that causes a specific disease or pathology associated with the kinase. Both the kinases of the present invention and appropriate variants and fragments can be used in high-throughput screens to assay candidate compounds for the ability to bind to the kinase. These compounds can be further screened against a functional kinase to determine the effect of the compound on the kinase activity. Further, these compounds can be tested in animal or

invertebrate systems to determine activity/effectiveness. Compounds can be identified that activate (agonist) or inactivate (antagonist) the kinase to a desired degree.

Further, the proteins of the present invention can be used to screen a compound for the ability to stimulate or inhibit interaction between the kinase protein and a molecule that normally interacts with the kinase protein, e.g. a substrate or a component of the signal pathway that the kinase protein normally interacts (for example, another kinase). Such assays typically include the steps of combining the kinase protein with a candidate compound under conditions that allow the kinase protein, or fragment, to interact with the target molecule, and to detect the formation of a complex between the protein and the target or to detect the biochemical consequence of the interaction with the kinase protein and the target, such as any of the associated effects of signal transduction such as protein phosphorylation, cAMP turnover, and adenylate cyclase activation, etc.

Candidate compounds include, for example, 1) peptides such as soluble peptides, including Ig-tailed fusion peptides and members of random peptide libraries (see, e.g., Lam *et al.*, *Nature 354*:82-84 (1991); Houghten *et al.*, *Nature 354*:84-86 (1991)) and combinatorial chemistry-derived molecular libraries made of D- and/or L- configuration amino acids; 2) phosphopeptides (e.g., members of random and partially degenerate, directed phosphopeptide libraries, see, e.g., Songyang *et al.*, *Cell 72*:767-778 (1993)); 3) antibodies (e.g., polyclonal, monoclonal, humanized, anti-idiotypic, chimeric, and single chain antibodies as well as Fab, $F(ab')_2$, Fab expression library fragments, and epitope-binding fragments of antibodies); and 4) small organic and inorganic molecules (e.g., molecules obtained from combinatorial and natural product libraries).

One candidate compound is a soluble fragment of the receptor that competes for substrate binding. Other candidate compounds include mutant kinases or appropriate fragments containing mutations that affect kinase function and thus compete for substrate. Accordingly, a fragment that competes for substrate, for example with a higher affinity, or a fragment that binds substrate but does not allow release, is encompassed by the invention.

The invention further includes other end point assays to identify compounds that modulate (stimulate or inhibit) kinase activity. The assays typically involve an assay of events in the signal transduction pathway that indicate kinase activity. Thus, the phosphorylation of a substrate, activation of a protein, a change in the expression of genes that are up- or down-regulated in response to the kinase protein dependent signal cascade can be assayed.

Any of the biological or biochemical functions mediated by the kinase can be used as an endpoint assay. These include all of the biochemical or biochemical/biological events described herein, in the references cited herein, incorporated by reference for these endpoint assay targets, and

other functions known to those of ordinary skill in the art or that can be readily identified using the information provided in the Figures, particularly Figure 2. Specifically, a biological function of a cell or tissues that expresses the kinase can be assayed. Experimental data as provided in Figure 1 indicates that kinase proteins of the present invention are expressed in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Specifically, a virtual northern blot shows expression in human colon carcinoma. In addition, PCR-based tissue screening panel indicates expression in human placenta, kidney, lung, skeletal muscle, heart, and fetal brain.

Binding and/or activating compounds can also be screened by using chimeric kinase proteins in which the amino terminal extracellular domain, or parts thereof, the entire transmembrane domain or subregions, such as any of the seven transmembrane segments or any of the intracellular or extracellular loops and the carboxy terminal intracellular domain, or parts thereof, can be replaced by heterologous domains or subregions. For example, a substrate-binding region can be used that interacts with a different substrate then that which is recognized by the native kinase. Accordingly, a different set of signal transduction components is available as an end-point assay for activation. This allows for assays to be performed in other than the specific host cell from which the kinase is derived.

The proteins of the present invention are also useful in competition binding assays in methods designed to discover compounds that interact with the kinase (e.g. binding partners and/or ligands). Thus, a compound is exposed to a kinase polypeptide under conditions that allow the compound to bind or to otherwise interact with the polypeptide. Soluble kinase polypeptide is also added to the mixture. If the test compound interacts with the soluble kinase polypeptide, it decreases the amount of complex formed or activity from the kinase target. This type of assay is particularly useful in cases in which compounds are sought that interact with specific regions of the kinase. Thus, the soluble polypeptide that competes with the target kinase region is designed to contain peptide sequences corresponding to the region of interest.

To perform cell free drug screening assays, it is sometimes desirable to immobilize either the kinase protein, or fragment, or its target molecule to facilitate separation of complexes from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay.

Techniques for immobilizing proteins on matrices can be used in the drug screening assays. In one embodiment, a fusion protein can be provided which adds a domain that allows the protein to be bound to a matrix. For example, glutathione-S-transferase fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre

plates, which are then combined with the cell lysates (e.g., ^{35}S-labeled) and the candidate compound, and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads are washed to remove any unbound label, and the matrix immobilized and radiolabel determined directly, or in the supernatant after the complexes are dissociated. Alternatively, the complexes can be dissociated from the matrix, separated by SDS-PAGE, and the level of kinase-binding protein found in the bead fraction quantitated from the gel using standard electrophoretic techniques. For example, either the polypeptide or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin using techniques well known in the art. Alternatively, antibodies reactive with the protein but which do not interfere with binding of the protein to its target molecule can be derivatized to the wells of the plate, and the protein trapped in the wells by antibody conjugation. Preparations of a kinase-binding protein and a candidate compound are incubated in the kinase protein-presenting wells and the amount of complex trapped in the well can be quantitated. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the kinase protein target molecule, or which are reactive with kinase protein and compete with the target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the target molecule.

Agents that modulate one of the kinases of the present invention can be identified using one or more of the above assays, alone or in combination. It is generally preferable to use a cell-based or cell free system first and then confirm activity in an animal or other model system. Such model systems are well known in the art and can readily be employed in this context.

Modulators of kinase protein activity identified according to these drug screening assays can be used to treat a subject with a disorder mediated by the kinase pathway, by treating cells or tissues that express the kinase. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. These methods of treatment include the steps of administering a modulator of kinase activity in a pharmaceutical composition to a subject in need of such treatment, the modulator being identified as described herein.

In yet another aspect of the invention, the kinase proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent

WO94/10300), to identify other proteins, which bind to or interact with the kinase and are involved in kinase activity. Such kinase-binding proteins are also likely to be involved in the propagation of signals by the kinase proteins or kinase targets as, for example, downstream elements of a kinase-mediated signaling pathway. Alternatively, such kinase-binding proteins are likely to be kinase inhibitors.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a kinase protein is fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo,* forming a kinase-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the kinase protein.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (e.g., a kinase-modulating agent, an antisense kinase nucleic acid molecule, a kinase-specific antibody, or a kinase-binding partner) can be used in an animal or other model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal or other model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

The kinase proteins of the present invention are also useful to provide a target for diagnosing a disease or predisposition to disease mediated by the peptide. Accordingly, the invention provides methods for detecting the presence, or levels of, the protein (or encoding mRNA) in a cell, tissue, or organism. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. The method involves contacting a biological sample with a compound capable of

interacting with the kinase protein such that the interaction can be detected. Such an assay can be provided in a single detection format or a multi-detection format such as an antibody chip array.

One agent for detecting a protein in a sample is an antibody capable of selectively binding to protein. A biological sample includes tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject.

The peptides of the present invention also provide targets for diagnosing active protein activity, disease, or predisposition to disease, in a patient having a variant peptide, particularly activities and conditions that are known for other members of the family of proteins to which the present one belongs. Thus, the peptide can be isolated from a biological sample and assayed for the presence of a genetic mutation that results in aberrant peptide. This includes amino acid substitution, deletion, insertion, rearrangement, (as the result of aberrant splicing events), and inappropriate post-translational modification. Analytic methods include altered electrophoretic mobility, altered tryptic peptide digest, altered kinase activity in cell-based or cell-free assay, alteration in substrate or antibody-binding pattern, altered isoelectric point, direct amino acid sequencing, and any other of the known assay techniques useful for detecting mutations in a protein. Such an assay can be provided in a single detection format or a multi-detection format such as an antibody chip array.

In vitro techniques for detection of peptide include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence using a detection reagent, such as an antibody or protein binding agent. Alternatively, the peptide can be detected *in vivo* in a subject by introducing into the subject a labeled anti-peptide antibody or other types of detection agent. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. Particularly useful are methods that detect the allelic variant of a peptide expressed in a subject and methods which detect fragments of a peptide in a sample.

The peptides are also useful in pharmacogenomic analysis. Pharmacogenomics deal with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, e.g., Eichelbaum, M. (*Clin. Exp. Pharmacol. Physiol.* 23(10-11):983-985 (1996)), and Linder, M.W. (*Clin. Chem.* 43(2):254-266 (1997)). The clinical outcomes of these variations result in severe toxicity of therapeutic drugs in certain individuals or therapeutic failure of drugs in certain individuals as a result of individual variation in metabolism. Thus, the genotype of the individual can determine the way a therapeutic compound acts on the body or the way the body metabolizes the compound. Further, the activity of drug metabolizing

enzymes effects both the intensity and duration of drug action. Thus, the pharmacogenomics of the individual permit the selection of effective compounds and effective dosages of such compounds for prophylactic or therapeutic treatment based on the individual's genotype. The discovery of genetic polymorphisms in some drug metabolizing enzymes has explained why some patients do not obtain the expected drug effects, show an exaggerated drug effect, or experience serious toxicity from standard drug dosages. Polymorphisms can be expressed in the phenotype of the extensive metabolizer and the phenotype of the poor metabolizer. Accordingly, genetic polymorphism may lead to allelic protein variants of the kinase protein in which one or more of the kinase functions in one population is different from those in another population. The peptides thus allow a target to ascertain a genetic predisposition that can affect treatment modality. Thus, in a ligand-based treatment, polymorphism may give rise to amino terminal extracellular domains and/or other substrate-binding regions that are more or less active in substrate binding, and kinase activation. Accordingly, substrate dosage would necessarily be modified to maximize the therapeutic effect within a given population containing a polymorphism. As an alternative to genotyping, specific polymorphic peptides could be identified.

The peptides are also useful for treating a disorder characterized by an absence of, inappropriate, or unwanted expression of the protein. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Accordingly, methods for treatment include the use of the kinase protein or fragments.

Antibodies

The invention also provides antibodies that selectively bind to one of the peptides of the present invention, a protein comprising such a peptide, as well as variants and fragments thereof. As used herein, an antibody selectively binds a target peptide when it binds the target peptide and does not significantly bind to unrelated proteins. An antibody is still considered to selectively bind a peptide even if it also binds to other proteins that are not substantially homologous with the target peptide so long as such proteins share homology with a fragment or domain of the peptide target of the antibody. In this case, it would be understood that antibody binding to the peptide is still selective despite some degree of cross-reactivity.

As used herein, an antibody is defined in terms consistent with that recognized within the art: they are multi-subunit proteins produced by a mammalian organism in response to an antigen challenge. The antibodies of the present invention include polyclonal antibodies and monoclonal

antibodies, as well as fragments of such antibodies, including, but not limited to, Fab or $F(ab')_2$, and Fv fragments.

Many methods are known for generating and/or identifying antibodies to a given target peptide. Several such methods are described by Harlow, Antibodies, Cold Spring Harbor Press, (1989).

In general, to generate antibodies, an isolated peptide is used as an immunogen and is administered to a mammalian organism, such as a rat, rabbit or mouse. The full-length protein, an antigenic peptide fragment or a fusion protein can be used. Particularly important fragments are those covering functional domains, such as the domains identified in Figure 2, and domain of sequence homology or divergence amongst the family, such as those that can readily be identified using protein alignment methods and as presented in the Figures.

Antibodies are preferably prepared from regions or discrete fragments of the kinase proteins. Antibodies can be prepared from any region of the peptide as described herein. However, preferred regions will include those involved in function/activity and/or kinase/binding partner interaction. Figure 2 can be used to identify particularly important regions while sequence alignment can be used to identify conserved and unique sequence fragments.

An antigenic fragment will typically comprise at least 8 contiguous amino acid residues. The antigenic peptide can comprise, however, at least 10, 12, 14, 16 or more amino acid residues. Such fragments can be selected on a physical property, such as fragments correspond to regions that are located on the surface of the protein, e.g., hydrophilic regions or can be selected based on sequence uniqueness (see Figure 2).

Detection on an antibody of the present invention can be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

Antibody Uses

The antibodies can be used to isolate one of the proteins of the present invention by standard techniques, such as affinity chromatography or immunoprecipitation. The antibodies can facilitate the purification of the natural protein from cells and recombinantly produced protein expressed in host cells. In addition, such antibodies are useful to detect the presence of one of the proteins of the present invention in cells or tissues to determine the pattern of expression of the protein among various tissues in an organism and over the course of normal development. Experimental data as provided in Figure 1 indicates that kinase proteins of the present invention are expressed in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Specifically, a virtual northern blot shows expression in human colon carcinoma. In addition, PCR-based tissue screening panel indicates expression in human placenta, kidney, lung, skeletal muscle, heart, and fetal brain. Further, such antibodies can be used to detect protein *in situ*, *in vitro*, or in a cell lysate or supernatant in order to evaluate the abundance and pattern of expression. Also, such antibodies can be used to assess abnormal tissue distribution or abnormal expression during development or progression of a biological condition. Antibody detection of circulating fragments of the full length protein can be used to identify turnover.

Further, the antibodies can be used to assess expression in disease states such as in active stages of the disease or in an individual with a predisposition toward disease related to the protein's function. When a disorder is caused by an inappropriate tissue distribution, developmental expression, level of expression of the protein, or expressed/processed form, the antibody can be prepared against the normal protein. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. If a disorder is characterized by a specific mutation in the protein, antibodies specific for this mutant protein can be used to assay for the presence of the specific mutant protein.

The antibodies can also be used to assess normal and aberrant subcellular localization of cells in the various tissues in an organism. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. The diagnostic uses can be applied, not only in genetic testing, but also in monitoring a treatment modality. Accordingly, where treatment is ultimately aimed at correcting expression level or the presence of aberrant sequence and aberrant tissue distribution or developmental expression, antibodies directed against the protein or relevant fragments can be used to monitor therapeutic efficacy.

Additionally, antibodies are useful in pharmacogenomic analysis. Thus, antibodies prepared against polymorphic proteins can be used to identify individuals that require modified treatment modalities. The antibodies are also useful as diagnostic tools as an immunological marker for aberrant protein analyzed by electrophoretic mobility, isoelectric point, tryptic peptide digest, and other physical assays known to those in the art.

The antibodies are also useful for tissue typing. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Thus, where a specific protein has been correlated with expression in a specific tissue, antibodies that are specific for this protein can be used to identify a tissue type.

The antibodies are also useful for inhibiting protein function, for example, blocking the binding of the kinase peptide to a binding partner such as a substrate. These uses can also be applied in a therapeutic context in which treatment involves inhibiting the protein's function. An antibody can be used, for example, to block binding, thus modulating (agonizing or antagonizing) the peptides activity. Antibodies can be prepared against specific fragments containing sites required for function or against intact protein that is associated with a cell or cell membrane. See Figure 2 for structural information relating to the proteins of the present invention.

The invention also encompasses kits for using antibodies to detect the presence of a protein in a biological sample. The kit can comprise antibodies such as a labeled or labelable antibody and a compound or agent for detecting protein in a biological sample; means for determining the amount of protein in the sample; means for comparing the amount of protein in the sample with a standard; and instructions for use. Such a kit can be supplied to detect a single protein or epitope or can be configured to detect one of a multitude of epitopes, such as in an antibody detection array. Arrays are described in detail below for nuleic acid arrays and similar methods have been developed for antibody arrays.

Nucleic Acid Molecules

The present invention further provides isolated nucleic acid molecules that encode a kinase peptide or protein of the present invention (cDNA, transcript and genomic sequence). Such nucleic acid molecules will consist of, consist essentially of, or comprise a nucleotide sequence that encodes one of the kinase peptides of the present invention, an allelic variant thereof, or an ortholog or paralog thereof.

As used herein, an "isolated" nucleic acid molecule is one that is separated from other nucleic acid present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. However, there can be some flanking nucleotide sequences, for example up to about 5KB, 4KB, 3KB, 2KB, or 1KB or less, particularly contiguous peptide encoding sequences and peptide encoding sequences within the same gene but separated by introns in the genomic sequence. The important point is that the nucleic acid is isolated from remote and unimportant flanking sequences such that it can be subjected to the specific manipulations described herein such as recombinant expression, preparation of probes and primers, and other uses specific to the nucleic acid sequences.

Moreover, an "isolated" nucleic acid molecule, such as a transcript/cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. However, the nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated.

For example, recombinant DNA molecules contained in a vector are considered isolated. Further examples of isolated DNA molecules include recombinant DNA molecules maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of the isolated DNA molecules of the present invention. Isolated nucleic acid molecules according to the present invention further include such molecules produced synthetically.

Accordingly, the present invention provides nucleic acid molecules that consist of the nucleotide sequence shown in Figure 1 or 3 (SEQ ID NO:1, transcript sequence and SEQ ID NO:3, genomic sequence), or any nucleic acid molecule that encodes the protein provided in Figure 2, SEQ ID NO:2. A nucleic acid molecule consists of a nucleotide sequence when the nucleotide sequence is the complete nucleotide sequence of the nucleic acid molecule.

The present invention further provides nucleic acid molecules that consist essentially of the nucleotide sequence shown in Figure 1 or 3 (SEQ ID NO:1, transcript sequence and SEQ ID NO:3, genomic sequence), or any nucleic acid molecule that encodes the protein provided in Figure 2, SEQ ID NO:2. A nucleic acid molecule consists essentially of a nucleotide sequence when such a nucleotide sequence is present with only a few additional nucleic acid residues in the final nucleic acid molecule.

The present invention further provides nucleic acid molecules that comprise the nucleotide sequences shown in Figure 1 or 3 (SEQ ID NO:1, transcript sequence and SEQ ID NO:3, genomic sequence), or any nucleic acid molecule that encodes the protein provided in Figure 2, SEQ ID NO:2. A nucleic acid molecule comprises a nucleotide sequence when the nucleotide sequence is at least part of the final nucleotide sequence of the nucleic acid molecule. In such a fashion, the nucleic acid molecule can be only the nucleotide sequence or have additional nucleic acid residues, such as nucleic acid residues that are naturally associated with it or heterologous nucleotide sequences. Such a nucleic acid molecule can have a few additional nucleotides or can comprises several hundred or more additional nucleotides. A brief description of how various types of these nucleic acid molecules can be readily made/isolated is provided below.

In Figures 1 and 3, both coding and non-coding sequences are provided. Because of the source of the present invention, humans genomic sequence (Figure 3) and cDNA/transcript sequences (Figure 1), the nucleic acid molecules in the Figures will contain genomic intronic sequences, 5' and 3' non-coding sequences, gene regulatory regions and non-coding intergenic sequences. In general such sequence features are either noted in Figures 1 and 3 or can readily be identified using computational tools known in the art. As discussed below, some of the non-coding regions, particularly gene regulatory elements such as promoters, are useful for a variety of purposes, e.g. control of heterologous gene expression, target for identifying gene activity modulating compounds, and are particularly claimed as fragments of the genomic sequence provided herein.

The isolated nucleic acid molecules can encode the mature protein plus additional amino or carboxyl-terminal amino acids, or amino acids interior to the mature peptide (when the mature form has more than one peptide chain, for instance). Such sequences may play a role in processing of a protein from precursor to a mature form, facilitate protein trafficking, prolong or shorten protein half-life or facilitate manipulation of a protein for assay or production, among other things. As generally is the case *in situ*, the additional amino acids may be processed away from the mature protein by cellular enzymes.

As mentioned above, the isolated nucleic acid molecules include, but are not limited to, the sequence encoding the kinase peptide alone, the sequence encoding the mature peptide and additional coding sequences, such as a leader or secretory sequence (e.g., a pre-pro or pro-protein sequence), the sequence encoding the mature peptide, with or without the additional coding sequences, plus additional non-coding sequences, for example introns and non-coding 5' and 3' sequences such as transcribed but non-translated sequences that play a role in transcription, mRNA

processing (including splicing and polyadenylation signals), ribosome binding and stability of mRNA. In addition, the nucleic acid molecule may be fused to a marker sequence encoding, for example, a peptide that facilitates purification.

Isolated nucleic acid molecules can be in the form of RNA, such as mRNA, or in the form DNA, including cDNA and genomic DNA obtained by cloning or produced by chemical synthetic techniques or by a combination thereof. The nucleic acid, especially DNA, can be double-stranded or single-stranded. Single-stranded nucleic acid can be the coding strand (sense strand) or the non-coding strand (anti-sense strand).

The invention further provides nucleic acid molecules that encode fragments of the peptides of the present invention as well as nucleic acid molecules that encode obvious variants of the kinase proteins of the present invention that are described above. Such nucleic acid molecules may be naturally occurring, such as allelic variants (same locus), paralogs (different locus), and orthologs (different organism), or may be constructed by recombinant DNA methods or by chemical synthesis. Such non-naturally occurring variants may be made by mutagenesis techniques, including those applied to nucleic acid molecules, cells, or organisms. Accordingly, as discussed above, the variants can contain nucleotide substitutions, deletions, inversions and insertions. Variation can occur in either or both the coding and non-coding regions. The variations can produce both conservative and non-conservative amino acid substitutions.

The present invention further provides non-coding fragments of the nucleic acid molecules provided in Figures 1 and 3. Preferred non-coding fragments include, but are not limited to, promoter sequences, enhancer sequences, gene modulating sequences and gene termination sequences. Such fragments are useful in controlling heterologous gene expression and in developing screens to identify gene-modulating agents. A promoter can readily be identified as being 5' to the ATG start site in the genomic sequence provided in Figure 3.

A fragment comprises a contiguous nucleotide sequence greater than 12 or more nucleotides. Further, a fragment could at least 30, 40, 50, 100, 250 or 500 nucleotides in length. The length of the fragment will be based on its intended use. For example, the fragment can encode epitope bearing regions of the peptide, or can be useful as DNA probes and primers. Such fragments can be isolated using the known nucleotide sequence to synthesize an oligonucleotide probe. A labeled probe can then be used to screen a cDNA library, genomic DNA library, or mRNA to isolate nucleic acid corresponding to the coding region. Further, primers can be used in PCR reactions to clone specific regions of gene.

A probe/primer typically comprises substantially a purified oligonucleotide or oligonucleotide pair. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 20, 25, 40, 50 or more consecutive nucleotides.

Orthologs, homologs, and allelic variants can be identified using methods well known in the art. As described in the Peptide Section, these variants comprise a nucleotide sequence encoding a peptide that is typically 60-70%, 70-80%, 80-90%, and more typically at least about 90-95% or more homologous to the nucleotide sequence shown in the Figure sheets or a fragment of this sequence. Such nucleic acid molecules can readily be identified as being able to hybridize under moderate to stringent conditions, to the nucleotide sequence shown in the Figure sheets or a fragment of the sequence. Allelic variants can readily be determined by genetic locus of the encoding gene. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 1 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention encoding a novel phosphatase maps to public BAC AC AC023889, which is known to be located on human chromosome 1.

Figure 3 provides information on SNPs that have been identified in a gene encoding the kinase protein of the present invention. 6 SNP variants were found, and all SNPs in exons, of which 3 of these cause changes in the amino acid sequence (i.e., nonsynonymous SNPs). The changes in the amino acid sequence that these SNPs cause is indicated in Figure 3 and can readily be determined using the universal genetic code and the protein sequence provided in Figure 2 as a reference.

As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences encoding a peptide at least 60-70% homologous to each other typically remain hybridized to each other. The conditions can be such that sequences at least about 60%, at least about 70%, or at least about 80% or more homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. One example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65C. Examples of moderate to low stringency hybridization conditions are well known in the art.

Nucleic Acid Molecule Uses

The nucleic acid molecules of the present invention are useful for probes, primers, chemical intermediates, and in biological assays. The nucleic acid molecules are useful as a hybridization probe for messenger RNA, transcript/cDNA and genomic DNA to isolate full-length cDNA and genomic clones encoding the peptide described in Figure 2 and to isolate cDNA and genomic clones that correspond to variants (alleles, orthologs, etc.) producing the same or related peptides shown in Figure 2. 6 SNPs, have been identified in the gene encoding the kinase protein provided by the present invention and are given in Figure 3.

The probe can correspond to any sequence along the entire length of the nucleic acid molecules provided in the Figures. Accordingly, it could be derived from 5' noncoding regions, the coding region, and 3' noncoding regions. However, as discussed, fragments are not to be construed as encompassing fragments disclosed prior to the present invention.

The nucleic acid molecules are also useful as primers for PCR to amplify any given region of a nucleic acid molecule and are useful to synthesize antisense molecules of desired length and sequence.

The nucleic acid molecules are also useful for constructing recombinant vectors. Such vectors include expression vectors that express a portion of, or all of, the peptide sequences. Vectors also include insertion vectors, used to integrate into another nucleic acid molecule sequence, such as into the cellular genome, to alter *in situ* expression of a gene and/or gene product. For example, an endogenous coding sequence can be replaced via homologous recombination with all or part of the coding region containing one or more specifically introduced mutations.

The nucleic acid molecules are also useful for expressing antigenic portions of the proteins.

The nucleic acid molecules are also useful as probes for determining the chromosomal positions of the nucleic acid molecules by means of *in situ* hybridization methods. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 1 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention encoding a novel phosphatase maps to public BAC AC AC023889, which is known to be located on human chromosome 1.

The nucleic acid molecules are also useful in making vectors containing the gene regulatory regions of the nucleic acid molecules of the present invention.

The nucleic acid molecules are also useful for designing ribozymes corresponding to all, or a part, of the mRNA produced from the nucleic acid molecules described herein.

The nucleic acid molecules are also useful for making vectors that express part, or all, of the peptides.

The nucleic acid molecules are also useful for constructing host cells expressing a part, or all, of the nucleic acid molecules and peptides.

The nucleic acid molecules are also useful for constructing transgenic animals expressing all, or a part, of the nucleic acid molecules and peptides.

The nucleic acid molecules are also useful as hybridization probes for determining the presence, level, form and distribution of nucleic acid expression. Experimental data as provided in Figure 1 indicates that kinase proteins of the present invention are expressed in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Specifically, a virtual northern blot shows expression in human colon carcinoma. In addition, PCR-based tissue screening panel indicates expression in human placenta, kidney, lung, skeletal muscle, heart, and fetal brain. Accordingly, the probes can be used to detect the presence of, or to determine levels of, a specific nucleic acid molecule in cells, tissues, and in organisms. The nucleic acid whose level is determined can be DNA or RNA. Accordingly, probes corresponding to the peptides described herein can be used to assess expression and/or gene copy number in a given cell, tissue, or organism. These uses are relevant for diagnosis of disorders involving an increase or decrease in kinase protein expression relative to normal results.

In vitro techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detecting DNA includes Southern hybridizations and *in situ* hybridization.

Probes can be used as a part of a diagnostic test kit for identifying cells or tissues that express a kinase protein, such as by measuring a level of a kinase-encoding nucleic acid in a sample of cells from a subject e.g., mRNA or genomic DNA, or determining if a kinase gene has been mutated. Experimental data as provided in Figure 1 indicates that kinase proteins of the present invention are expressed in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Specifically, a virtual northern blot shows expression in human colon carcinoma. In addition, PCR-based tissue screening panel indicates expression in human placenta, kidney, lung, skeletal muscle, heart, and fetal brain.

Nucleic acid expression assays are useful for drug screening to identify compounds that modulate kinase nucleic acid expression.

The invention thus provides a method for identifying a compound that can be used to treat a disorder associated with nucleic acid expression of the kinase gene, particularly biological and

pathological processes that are mediated by the kinase in cells and tissues that express it. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. The method typically includes assaying the ability of the compound to modulate the expression of the kinase nucleic acid and thus identifying a compound that can be used to treat a disorder characterized by undesired kinase nucleic acid expression. The assays can be performed in cell-based and cell-free systems. Cell-based assays include cells naturally expressing the kinase nucleic acid or recombinant cells genetically engineered to express specific nucleic acid sequences.

The assay for kinase nucleic acid expression can involve direct assay of nucleic acid levels, such as mRNA levels, or on collateral compounds involved in the signal pathway. Further, the expression of genes that are up- or down-regulated in response to the kinase protein signal pathway can also be assayed. In this embodiment the regulatory regions of these genes can be operably linked to a reporter gene such as luciferase.

Thus, modulators of kinase gene expression can be identified in a method wherein a cell is contacted with a candidate compound and the expression of mRNA determined. The level of expression of kinase mRNA in the presence of the candidate compound is compared to the level of expression of kinase mRNA in the absence of the candidate compound. The candidate compound can then be identified as a modulator of nucleic acid expression based on this comparison and be used, for example to treat a disorder characterized by aberrant nucleic acid expression. When expression of mRNA is statistically significantly greater in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of nucleic acid expression. When nucleic acid expression is statistically significantly less in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of nucleic acid expression.

The invention further provides methods of treatment, with the nucleic acid as a target, using a compound identified through drug screening as a gene modulator to modulate kinase nucleic acid expression in cells and tissues that express the kinase. Experimental data as provided in Figure 1 indicates that kinase proteins of the present invention are expressed in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Specifically, a virtual northern blot shows expression in human colon carcinoma. In addition, PCR-based tissue screening panel indicates expression in human placenta, kidney, lung, skeletal muscle, heart, and fetal brain. Modulation includes both up-regulation (i.e. activation or agonization) or down-regulation (suppression or antagonization) or nucleic acid expression.

Alternatively, a modulator for kinase nucleic acid expression can be a small molecule or drug identified using the screening assays described herein as long as the drug or small molecule inhibits the kinase nucleic acid expression in the cells and tissues that express the protein. Experimental data as provided in Figure 1 indicates expression in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma.

The nucleic acid molecules are also useful for monitoring the effectiveness of modulating compounds on the expression or activity of the kinase gene in clinical trials or in a treatment regimen. Thus, the gene expression pattern can serve as a barometer for the continuing effectiveness of treatment with the compound, particularly with compounds to which a patient can develop resistance. The gene expression pattern can also serve as a marker indicative of a physiological response of the affected cells to the compound. Accordingly, such monitoring would allow either increased administration of the compound or the administration of alternative compounds to which the patient has not become resistant. Similarly, if the level of nucleic acid expression falls below a desirable level, administration of the compound could be commensurately decreased.

The nucleic acid molecules are also useful in diagnostic assays for qualitative changes in kinase nucleic acid expression, and particularly in qualitative changes that lead to pathology. The nucleic acid molecules can be used to detect mutations in kinase genes and gene expression products such as mRNA. The nucleic acid molecules can be used as hybridization probes to detect naturally occurring genetic mutations in the kinase gene and thereby to determine whether a subject with the mutation is at risk for a disorder caused by the mutation. Mutations include deletion, addition, or substitution of one or more nucleotides in the gene, chromosomal rearrangement, such as inversion or transposition, modification of genomic DNA, such as aberrant methylation patterns or changes in gene copy number, such as amplification. Detection of a mutated form of the kinase gene associated with a dysfunction provides a diagnostic tool for an active disease or susceptibility to disease when the disease results from overexpression, underexpression, or altered expression of a kinase protein.

Individuals carrying mutations in the kinase gene can be detected at the nucleic acid level by a variety of techniques. Figure 3 provides information on SNPs that have been identified in a gene encoding the kinase protein of the present invention. 6 SNP variants were found, and all SNPs in exons, of which 3 of these cause changes in the amino acid sequence (i.e., nonsynonymous SNPs). The changes in the amino acid sequence that these SNPs cause is indicated in Figure 3 and can readily be determined using the universal genetic code and the protein sequence provided in Figure

2 as a reference. As indicated by the data presented in Figure 3, the map position was determined to be on chromosome 1 by ePCR, and confirmed with radiation hybrid mapping. As indicated by the data presented in Figure 3, the gene provided by the present invention encoding a novel phosphatase maps to public BAC AC AC023889, which is known to be located on human chromosome 1.

Genomic DNA can be analyzed directly or can be amplified by using PCR prior to analysis. RNA or cDNA can be used in the same way. In some uses, detection of the mutation involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran *et al.*, *Science 241*:1077-1080 (1988); and Nakazawa *et al.*, *PNAS 91*:360-364 (1994)), the latter of which can be particularly useful for detecting point mutations in the gene (see Abravaya *et al.*, *Nucleic Acids Res. 23*:675-682 (1995)). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a gene under conditions such that hybridization and amplification of the gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. Deletions and insertions can be detected by a change in size of the amplified product compared to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to normal RNA or antisense DNA sequences.

Alternatively, mutations in a kinase gene can be directly identified, for example, by alterations in restriction enzyme digestion patterns determined by gel electrophoresis.

Further, sequence-specific ribozymes (U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site. Perfectly matched sequences can be distinguished from mismatched sequences by nuclease cleavage digestion assays or by differences in melting temperature.

Sequence changes at specific locations can also be assessed by nuclease protection assays such as RNase and S1 protection or the chemical cleavage method. Furthermore, sequence differences between a mutant kinase gene and a wild-type gene can be determined by direct DNA sequencing. A variety of automated sequencing procedures can be utilized when performing the diagnostic assays (Naeve, C.W., (1995) *Biotechniques 19*:448), including sequencing by mass spectrometry (see, e.g., PCT International Publication No. WO 94/16101; Cohen *et al.*, *Adv. Chromatogr. 36*:127-162 (1996); and Griffin *et al.*, *Appl. Biochem. Biotechnol. 38*:147-159 (1993)).

Other methods for detecting mutations in the gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA duplexes (Myers *et al.*, *Science 230*:1242 (1985)); Cotton *et al.*, *PNAS 85*:4397 (1988); Saleeba *et al.*, *Meth. Enzymol. 217*:286-295 (1992)), electrophoretic mobility of mutant and wild type nucleic acid is compared (Orita *et al.*, *PNAS 86*:2766 (1989); Cotton *et al.*, *Mutat. Res. 285*:125-144 (1993); and Hayashi *et al.*, *Genet. Anal. Tech. Appl. 9*:73-79 (1992)), and movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (Myers *et al.*, *Nature 313*:495 (1985)). Examples of other techniques for detecting point mutations include selective oligonucleotide hybridization, selective amplification, and selective primer extension.

The nucleic acid molecules are also useful for testing an individual for a genotype that while not necessarily causing the disease, nevertheless affects the treatment modality. Thus, the nucleic acid molecules can be used to study the relationship between an individual's genotype and the individual's response to a compound used for treatment (pharmacogenomic relationship). Accordingly, the nucleic acid molecules described herein can be used to assess the mutation content of the kinase gene in an individual in order to select an appropriate compound or dosage regimen for treatment. Figure 3 provides information on SNPs that have been identified in a gene encoding the kinase protein of the present invention. 6 SNP variants were found, and all SNPs in exons, of which 3 of these cause changes in the amino acid sequence (i.e., nonsynonymous SNPs). The changes in the amino acid sequence that these SNPs cause is indicated in Figure 3 and can readily be determined using the universal genetic code and the protein sequence provided in Figure 2 as a reference.

Thus nucleic acid molecules displaying genetic variations that affect treatment provide a diagnostic target that can be used to tailor treatment in an individual. Accordingly, the production of recombinant cells and animals containing these polymorphisms allow effective clinical design of treatment compounds and dosage regimens.

The nucleic acid molecules are thus useful as antisense constructs to control kinase gene expression in cells, tissues, and organisms. A DNA antisense nucleic acid molecule is designed to be complementary to a region of the gene involved in transcription, preventing transcription and hence production of kinase protein. An antisense RNA or DNA nucleic acid molecule would hybridize to the mRNA and thus block translation of mRNA into kinase protein.

Alternatively, a class of antisense molecules can be used to inactivate mRNA in order to decrease expression of kinase nucleic acid. Accordingly, these molecules can treat a disorder

characterized by abnormal or undesired kinase nucleic acid expression. This technique involves cleavage by means of ribozymes containing nucleotide sequences complementary to one or more regions in the mRNA that attenuate the ability of the mRNA to be translated. Possible regions include coding regions and particularly coding regions corresponding to the catalytic and other functional activities of the kinase protein, such as substrate binding.

The nucleic acid molecules also provide vectors for gene therapy in patients containing cells that are aberrant in kinase gene expression. Thus, recombinant cells, which include the patient's cells that have been engineered *ex vivo* and returned to the patient, are introduced into an individual where the cells produce the desired kinase protein to treat the individual.

The invention also encompasses kits for detecting the presence of a kinase nucleic acid in a biological sample. Experimental data as provided in Figure 1 indicates that kinase proteins of the present invention are expressed in the human placenta, kidney, lung, skeletal muscle, heart, fetal brain, and colon carcinoma. Specifically, a virtual northern blot shows expression in human colon carcinoma. In addition, PCR-based tissue screening panel indicates expression in human placenta, kidney, lung, skeletal muscle, heart, and fetal brain. For example, the kit can comprise reagents such as a labeled or labelable nucleic acid or agent capable of detecting kinase nucleic acid in a biological sample; means for determining the amount of kinase nucleic acid in the sample; and means for comparing the amount of kinase nucleic acid in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect kinase protein mRNA or DNA.

Nucleic Acid Arrays

The present invention further provides nucleic acid detection kits, such as arrays or microarrays of nucleic acid molecules that are based on the sequence information provided in Figures 1 and 3 (SEQ ID NOS:1 and 3).

As used herein "Arrays" or "Microarrays" refers to an array of distinct polynucleotides or oligonucleotides synthesized on a substrate, such as paper, nylon or other type of membrane, filter, chip, glass slide, or any other suitable solid support. In one embodiment, the microarray is prepared and used according to the methods described in US Patent 5,837,832, Chee *et al.*, PCT application W095/11995 (Chee *et al.*), Lockhart, D. J. *et al.* (1996; Nat. Biotech. 14: 1675-1680) and Schena, M. *et al.* (1996; Proc. Natl. Acad. Sci. 93: 10614-10619), all of which are incorporated herein in their entirety by reference. In other embodiments, such arrays are produced by the methods described by Brown *et al.*, US Patent No. 5,807,522.

The microarray or detection kit is preferably composed of a large number of unique, single-stranded nucleic acid sequences, usually either synthetic antisense oligonucleotides or fragments of cDNAs, fixed to a solid support. The oligonucleotides are preferably about 6-60 nucleotides in length, more preferably 15-30 nucleotides in length, and most preferably about 20-25 nucleotides in length. For a certain type of microarray or detection kit, it may be preferable to use oligonucleotides that are only 7-20 nucleotides in length. The microarray or detection kit may contain oligonucleotides that cover the known 5', or 3', sequence, sequential oligonucleotides which cover the full length sequence; or unique oligonucleotides selected from particular areas along the length of the sequence. Polynucleotides used in the microarray or detection kit may be oligonucleotides that are specific to a gene or genes of interest.

In order to produce oligonucleotides to a known sequence for a microarray or detection kit, the gene(s) of interest (or an ORF identified from the contigs of the present invention) is typically examined using a computer algorithm which starts at the 5' or at the 3' end of the nucleotide sequence. Typical algorithms will then identify oligomers of defined length that are unique to the gene, have a GC content within a range suitable for hybridization, and lack predicted secondary structure that may interfere with hybridization. In certain situations it may be appropriate to use pairs of oligonucleotides on a microarray or detection kit. The "pairs" will be identical, except for one nucleotide that preferably is located in the center of the sequence. The second oligonucleotide in the pair (mismatched by one) serves as a control. The number of oligonucleotide pairs may range from two to one million. The oligomers are synthesized at designated areas on a substrate using a light-directed chemical process. The substrate may be paper, nylon or other type of membrane, filter, chip, glass slide or any other suitable solid support.

In another aspect, an oligonucleotide may be synthesized on the surface of the substrate by using a chemical coupling procedure and an ink jet application apparatus, as described in PCT application W095/251116 (Baldeschweiler *et al.*) which is incorporated herein in its entirety by reference. In another aspect, a "gridded" array analogous to a dot (or slot) blot may be used to arrange and link cDNA fragments or oligonucleotides to the surface of a substrate using a vacuum system, thermal, UV, mechanical or chemical bonding procedures. An array, such as those described above, may be produced by hand or by using available devices (slot blot or dot blot apparatus), materials (any suitable solid support), and machines (including robotic instruments), and may contain 8, 24, 96, 384, 1536, 6144 or more oligonucleotides, or any other

number between two and one million which lends itself to the efficient use of commercially available instrumentation.

In order to conduct sample analysis using a microarray or detection kit, the RNA or DNA from a biological sample is made into hybridization probes. The mRNA is isolated, and cDNA is produced and used as a template to make antisense RNA (aRNA). The aRNA is amplified in the presence of fluorescent nucleotides, and labeled probes are incubated with the microarray or detection kit so that the probe sequences hybridize to complementary oligonucleotides of the microarray or detection kit. Incubation conditions are adjusted so that hybridization occurs with precise complementary matches or with various degrees of less complementarity. After removal of nonhybridized probes, a scanner is used to determine the levels and patterns of fluorescence. The scanned images are examined to determine degree of complementarity and the relative abundance of each oligonucleotide sequence on the microarray or detection kit. The biological samples may be obtained from any bodily fluids (such as blood, urine, saliva, phlegm, gastric juices, etc.), cultured cells, biopsies, or other tissue preparations. A detection system may be used to measure the absence, presence, and amount of hybridization for all of the distinct sequences simultaneously. This data may be used for large-scale correlation studies on the sequences, expression patterns, mutations, variants, or polymorphisms among samples.

Using such arrays, the present invention provides methods to identify the expression of the kinase proteins/peptides of the present invention. In detail, such methods comprise incubating a test sample with one or more nucleic acid molecules and assaying for binding of the nucleic acid molecule with components within the test sample. Such assays will typically involve arrays comprising many genes, at least one of which is a gene of the present invention and or alleles of the kinase gene of the present invention. Figure 3 provides information on SNPs that have been identified in a gene encoding the kinase protein of the present invention. 6 SNP variants were found, and all SNPs in exons, of which 3 of these cause changes in the amino acid sequence (i.e., nonsynonymous SNPs). The changes in the amino acid sequence that these SNPs cause is indicated in Figure 3 and can readily be determined using the universal genetic code and the protein sequence provided in Figure 2 as a reference.

Conditions for incubating a nucleic acid molecule with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid molecule used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification or array assay formats can readily be adapted to employ the novel fragments of the Human genome disclosed

herein. Examples of such assays can be found in Chard, T, *An Introduction to Radioimmunoassay and Related Techniques,* Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G. R. *et al., Techniques in Immunocytochemistry,* Academic Press, Orlando, FL Vol. 1 (1 982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., *Practice and Theory of Enzyme Immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology,* Elsevier Science Publishers, Amsterdam, The Netherlands (1985).

The test samples of the present invention include cells, protein or membrane extracts of cells. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing nucleic acid extracts or of cells are well known in the art and can be readily be adapted in order to obtain a sample that is compatible with the system utilized.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention.

Specifically, the invention provides a compartmentalized kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the nucleic acid molecules that can bind to a fragment of the Human genome disclosed herein; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound nucleic acid.

In detail, a compartmentalized kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers, strips of plastic, glass or paper, or arraying material such as silica. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the nucleic acid probe, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound probe. One skilled in the art will readily recognize that the previously unidentified kinase gene of the present invention can be routinely identified using the sequence information disclosed herein can be readily incorporated into one of the established kit formats which are well known in the art, particularly expression arrays.

Vectors/host cells

The invention also provides vectors containing the nucleic acid molecules described herein. The term "vector" refers to a vehicle, preferably a nucleic acid molecule, which can transport the nucleic acid molecules. When the vector is a nucleic acid molecule, the nucleic acid molecules are covalently linked to the vector nucleic acid. With this aspect of the invention, the vector includes a plasmid, single or double stranded phage, a single or double stranded RNA or DNA viral vector, or artificial chromosome, such as a BAC, PAC, YAC, OR MAC.

A vector can be maintained in the host cell as an extrachromosomal element where it replicates and produces additional copies of the nucleic acid molecules. Alternatively, the vector may integrate into the host cell genome and produce additional copies of the nucleic acid molecules when the host cell replicates.

The invention provides vectors for the maintenance (cloning vectors) or vectors for expression (expression vectors) of the nucleic acid molecules. The vectors can function in prokaryotic or eukaryotic cells or in both (shuttle vectors).

Expression vectors contain cis-acting regulatory regions that are operably linked in the vector to the nucleic acid molecules such that transcription of the nucleic acid molecules is allowed in a host cell. The nucleic acid molecules can be introduced into the host cell with a separate nucleic acid molecule capable of affecting transcription. Thus, the second nucleic acid molecule may provide a trans-acting factor interacting with the cis-regulatory control region to allow transcription of the nucleic acid molecules from the vector. Alternatively, a trans-acting factor may be supplied by the host cell. Finally, a trans-acting factor can be produced from the vector itself. It is understood, however, that in some embodiments, transcription and/or translation of the nucleic acid molecules can occur in a cell-free system.

The regulatory sequence to which the nucleic acid molecules described herein can be operably linked include promoters for directing mRNA transcription. These include, but are not limited to, the left promoter from bacteriophage λ, the lac, TRP, and TAC promoters from *E. coli*, the early and late promoters from SV40, the CMV immediate early promoter, the adenovirus early and late promoters, and retrovirus long-terminal repeats.

In addition to control regions that promote transcription, expression vectors may also include regions that modulate transcription, such as repressor binding sites and enhancers. Examples include the SV40 enhancer, the cytomegalovirus immediate early enhancer, polyoma enhancer, adenovirus enhancers, and retrovirus LTR enhancers.

In addition to containing sites for transcription initiation and control, expression vectors can also contain sequences necessary for transcription termination and, in the transcribed region a ribosome binding site for translation. Other regulatory control elements for expression include initiation and termination codons as well as polyadenylation signals. The person of ordinary skill in the art would be aware of the numerous regulatory sequences that are useful in expression vectors. Such regulatory sequences are described, for example, in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd. ed.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989).

A variety of expression vectors can be used to express a nucleic acid molecule. Such vectors include chromosomal, episomal, and virus-derived vectors, for example vectors derived from bacterial plasmids, from bacteriophage, from yeast episomes, from yeast chromosomal elements, including yeast artificial chromosomes, from viruses such as baculoviruses, papovaviruses such as SV40, Vaccinia viruses, adenoviruses, poxviruses, pseudorabies viruses, and retroviruses. Vectors may also be derived from combinations of these sources such as those derived from plasmid and bacteriophage genetic elements, e.g. cosmids and phagemids. Appropriate cloning and expression vectors for prokaryotic and eukaryotic hosts are described in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd. ed.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989).

The regulatory sequence may provide constitutive expression in one or more host cells (i.e. tissue specific) or may provide for inducible expression in one or more cell types such as by temperature, nutrient additive, or exogenous factor such as a hormone or other ligand. A variety of vectors providing for constitutive and inducible expression in prokaryotic and eukaryotic hosts are well known to those of ordinary skill in the art.

The nucleic acid molecules can be inserted into the vector nucleic acid by well-known methodology. Generally, the DNA sequence that will ultimately be expressed is joined to an expression vector by cleaving the DNA sequence and the expression vector with one or more restriction enzymes and then ligating the fragments together. Procedures for restriction enzyme digestion and ligation are well known to those of ordinary skill in the art.

The vector containing the appropriate nucleic acid molecule can be introduced into an appropriate host cell for propagation or expression using well-known techniques. Bacterial cells include, but are not limited to, *E. coli*, *Streptomyces*, and *Salmonella typhimurium*. Eukaryotic cells include, but are not limited to, yeast, insect cells such as *Drosophila*, animal cells such as COS and CHO cells, and plant cells.

As described herein, it may be desirable to express the peptide as a fusion protein. Accordingly, the invention provides fusion vectors that allow for the production of the peptides. Fusion vectors can increase the expression of a recombinant protein, increase the solubility of the recombinant protein, and aid in the purification of the protein by acting for example as a ligand for affinity purification. A proteolytic cleavage site may be introduced at the junction of the fusion moiety so that the desired peptide can ultimately be separated from the fusion moiety. Proteolytic enzymes include, but are not limited to, factor Xa, thrombin, and enterokinase. Typical fusion expression vectors include pGEX (Smith *et al.*, *Gene 67*:31-40 (1988)), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein. Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, *Gene 69*:301-315 (1988)) and pET 11d (Studier *et al.*, *Gene Expression Technology: Methods in Enzymology 185*:60-89 (1990)).

Recombinant protein expression can be maximized in host bacteria by providing a genetic background wherein the host cell has an impaired capacity to proteolytically cleave the recombinant protein. (Gottesman, S., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Alternatively, the sequence of the nucleic acid molecule of interest can be altered to provide preferential codon usage for a specific host cell, for example *E. coli*. (Wada *et al.*, *Nucleic Acids Res. 20*:2111-2118 (1992)).

The nucleic acid molecules can also be expressed by expression vectors that are operative in yeast. Examples of vectors for expression in yeast e.g., *S. cerevisiae* include pYepSec1 (Baldari, *et al.*, *EMBO J. 6*:229-234 (1987)), pMFa (Kurjan *et al.*, *Cell 30*:933-943(1982)), pJRY88 (Schultz *et al.*, *Gene 54*:113-123 (1987)), and pYES2 (Invitrogen Corporation, San Diego, CA).

The nucleic acid molecules can also be expressed in insect cells using, for example, baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith *et al.*, *Mol. Cell Biol. 3*:2156-2165 (1983)) and the pVL series (Lucklow *et al.*, *Virology 170*:31-39 (1989)).

In certain embodiments of the invention, the nucleic acid molecules described herein are expressed in mammalian cells using mammalian expression vectors. Examples of mammalian expression vectors include pCDM8 (Seed, B. *Nature 329*:840(1987)) and pMT2PC (Kaufman *et al.*, *EMBO J. 6*:187-195 (1987)).

The expression vectors listed herein are provided by way of example only of the well-known vectors available to those of ordinary skill in the art that would be useful to express the

nucleic acid molecules. The person of ordinary skill in the art would be aware of other vectors suitable for maintenance propagation or expression of the nucleic acid molecules described herein. These are found for example in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

The invention also encompasses vectors in which the nucleic acid sequences described herein are cloned into the vector in reverse orientation, but operably linked to a regulatory sequence that permits transcription of antisense RNA. Thus, an antisense transcript can be produced to all, or to a portion, of the nucleic acid molecule sequences described herein, including both coding and non-coding regions. Expression of this antisense RNA is subject to each of the parameters described above in relation to expression of the sense RNA (regulatory sequences, constitutive or inducible expression, tissue-specific expression).

The invention also relates to recombinant host cells containing the vectors described herein. Host cells therefore include prokaryotic cells, lower eukaryotic cells such as yeast, other eukaryotic cells such as insect cells, and higher eukaryotic cells such as mammalian cells.

The recombinant host cells are prepared by introducing the vector constructs described herein into the cells by techniques readily available to the person of ordinary skill in the art. These include, but are not limited to, calcium phosphate transfection, DEAE-dextran-mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, lipofection, and other techniques such as those found in Sambrook, *et al.* (*Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Host cells can contain more than one vector. Thus, different nucleotide sequences can be introduced on different vectors of the same cell. Similarly, the nucleic acid molecules can be introduced either alone or with other nucleic acid molecules that are not related to the nucleic acid molecules such as those providing trans-acting factors for expression vectors. When more than one vector is introduced into a cell, the vectors can be introduced independently, co-introduced or joined to the nucleic acid molecule vector.

In the case of bacteriophage and viral vectors, these can be introduced into cells as packaged or encapsulated virus by standard procedures for infection and transduction. Viral vectors can be replication-competent or replication-defective. In the case in which viral replication is defective, replication will occur in host cells providing functions that complement the defects.

Vectors generally include selectable markers that enable the selection of the subpopulation of cells that contain the recombinant vector constructs. The marker can be contained in the same vector that contains the nucleic acid molecules described herein or may be on a separate vector. Markers include tetracycline or ampicillin-resistance genes for prokaryotic host cells and dihydrofolate reductase or neomycin resistance for eukaryotic host cells. However, any marker that provides selection for a phenotypic trait will be effective.

While the mature proteins can be produced in bacteria, yeast, mammalian cells, and other cells under the control of the appropriate regulatory sequences, cell- free transcription and translation systems can also be used to produce these proteins using RNA derived from the DNA constructs described herein.

Where secretion of the peptide is desired, which is difficult to achieve with multi-transmembrane domain containing proteins such as kinases, appropriate secretion signals are incorporated into the vector. The signal sequence can be endogenous to the peptides or heterologous to these peptides.

Where the peptide is not secreted into the medium, which is typically the case with kinases, the protein can be isolated from the host cell by standard disruption procedures, including freeze thaw, sonication, mechanical disruption, use of lysing agents and the like. The peptide can then be recovered and purified by well-known purification methods including ammonium sulfate precipitation, acid extraction, anion or cationic exchange chromatography, phosphocellulose chromatography, hydrophobic-interaction chromatography, affinity chromatography, hydroxylapatite chromatography, lectin chromatography, or high performance liquid chromatography.

It is also understood that depending upon the host cell in recombinant production of the peptides described herein, the peptides can have various glycosylation patterns, depending upon the cell, or maybe non-glycosylated as when produced in bacteria. In addition, the peptides may include an initial modified methionine in some cases as a result of a host-mediated process.

Uses of vectors and host cells

The recombinant host cells expressing the peptides described herein have a variety of uses. First, the cells are useful for producing a kinase protein or peptide that can be further purified to produce desired amounts of kinase protein or fragments. Thus, host cells containing expression vectors are useful for peptide production.

Host cells are also useful for conducting cell-based assays involving the kinase protein or kinase protein fragments, such as those described above as well as other formats known in the art. Thus, a recombinant host cell expressing a native kinase protein is useful for assaying compounds that stimulate or inhibit kinase protein function.

Host cells are also useful for identifying kinase protein mutants in which these functions are affected. If the mutants naturally occur and give rise to a pathology, host cells containing the mutations are useful to assay compounds that have a desired effect on the mutant kinase protein (for example, stimulating or inhibiting function) which may not be indicated by their effect on the native kinase protein.

Genetically engineered host cells can be further used to produce non-human transgenic animals. A transgenic animal is preferably a mammal, for example a rodent, such as a rat or mouse, in which one or more of the cells of the animal include a transgene. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal in one or more cell types or tissues of the transgenic animal. These animals are useful for studying the function of a kinase protein and identifying and evaluating modulators of kinase protein activity. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, and amphibians.

A transgenic animal can be produced by introducing nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Any of the kinase protein nucleotide sequences can be introduced as a transgene into the genome of a non-human animal, such as a mouse.

Any of the regulatory or other sequences useful in expression vectors can form part of the transgenic sequence. This includes intronic sequences and polyadenylation signals, if not already included. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the kinase protein to particular cells.

Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo,* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of transgenic mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals

carrying the transgene. Moreover, transgenic animals carrying a transgene can further be bred to other transgenic animals carrying other transgenes. A transgenic animal also includes animals in which the entire animal or tissues in the animal have been produced using the homologously recombinant host cells described herein.

In another embodiment, transgenic non-human animals can be produced which contain selected systems that allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, e.g., Lakso *et al. PNAS 89*:6232-6236 (1992). Another example of a recombinase system is the FLP recombinase system of *S. cerevisiae* (O'Gorman *et al. Science 251*:1351-1355 (1991). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein is required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al. Nature 385*:810-813 (1997) and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, e.g., a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G_0 phase. The quiescent cell can then be fused, e.g., through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyst and then transferred to pseudopregnant female foster animal. The offspring born of this female foster animal will be a clone of the animal from which the cell, e.g., the somatic cell, is isolated.

Transgenic animals containing recombinant cells that express the peptides described herein are useful to conduct the assays described herein in an *in vivo* context. Accordingly, the various physiological factors that are present *in vivo* and that could effect substrate binding, kinase protein activation, and signal transduction, may not be evident from *in vitro* cell-free or cell-based assays. Accordingly, it is useful to provide non-human transgenic animals to assay *in vivo* kinase protein function, including substrate interaction, the effect of specific mutant kinase proteins on kinase protein function and substrate interaction, and the effect of chimeric kinase proteins. It is also possible to assess the effect of null mutations, that is, mutations that substantially or completely eliminate one or more kinase protein functions.

All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the above-described modes for carrying out the invention which are obvious to those skilled in the field of molecular biology or related fields are intended to be within the scope of the following claims.

Claims

That which is claimed is:

1. An isolated peptide consisting of an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence shown in SEQ ID NO:2;

(b) an amino acid sequence of an allelic variant of an amino acid sequence shown in SEQ ID NO:2, wherein said allelic variant is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(c) an amino acid sequence of an ortholog of an amino acid sequence shown in SEQ ID NO:2, wherein said ortholog is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3; and

(d) a fragment of an amino acid sequence shown in SEQ ID NO:2, wherein said fragment comprises at least 10 contiguous amino acids.

2. An isolated peptide comprising an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence shown in SEQ ID NO:2;

(b) an amino acid sequence of an allelic variant of an amino acid sequence shown in SEQ ID NO:2, wherein said allelic variant is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(c) an amino acid sequence of an ortholog of an amino acid sequence shown in SEQ ID NO:2, wherein said ortholog is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3; and

(d) a fragment of an amino acid sequence shown in SEQ ID NO:2, wherein said fragment comprises at least 10 contiguous amino acids.

3. An isolated antibody that selectively binds to a peptide of claim 2.

4. An isolated nucleic acid molecule consisting of a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes an amino acid sequence shown in SEQ ID NO:2;

(b) a nucleotide sequence that encodes of an allelic variant of an amino acid sequence shown in SEQ ID NO:2, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(c) a nucleotide sequence that encodes an ortholog of an amino acid sequence shown in SEQ ID NO:2, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(d) a nucleotide sequence that encodes a fragment of an amino acid sequence shown in SEQ ID NO:2, wherein said fragment comprises at least 10 contiguous amino acids; and

(e) a nucleotide sequence that is the complement of a nucleotide sequence of (a)-(d).

5. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes an amino acid sequence shown in SEQ ID NO:2;

(b) a nucleotide sequence that encodes of an allelic variant of an amino acid sequence shown in SEQ ID NO:2, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(c) a nucleotide sequence that encodes an ortholog of an amino acid sequence shown in SEQ ID NO:2, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule shown in SEQ ID NOS:1 or 3;

(d) a nucleotide sequence that encodes a fragment of an amino acid sequence shown in SEQ ID NO:2, wherein said fragment comprises at least 10 contiguous amino acids; and

(e) a nucleotide sequence that is the complement of a nucleotide sequence of (a)-(d).

6. A gene chip comprising a nucleic acid molecule of claim 5.

7. A transgenic non-human animal comprising a nucleic acid molecule of claim 5.

8. A nucleic acid vector comprising a nucleic acid molecule of claim 5.

9. A host cell containing the vector of claim 8.

10. A method for producing any of the peptides of claim 1 comprising introducing a nucleotide sequence encoding any of the amino acid sequences in (a)-(d) into a host cell, and culturing the host cell under conditions in which the peptides are expressed from the nucleotide sequence.

11. A method for producing any of the peptides of claim 2 comprising introducing a nucleotide sequence encoding any of the amino acid sequences in (a)-(d) into a host cell, and culturing the host cell under conditions in which the peptides are expressed from the nucleotide sequence.

12. A method for detecting the presence of any of the peptides of claim 2 in a sample, said method comprising contacting said sample with a detection agent that specifically allows detection of the presence of the peptide in the sample and then detecting the presence of the peptide.

13. A method for detecting the presence of a nucleic acid molecule of claim 5 in a sample, said method comprising contacting the sample with an oligonucleotide that hybridizes to said nucleic acid molecule under stringent conditions and determining whether the oligonucleotide binds to said nucleic acid molecule in the sample.

14. A method for identifying a modulator of a peptide of claim 2, said method comprising contacting said peptide with an agent and determining if said agent has modulated the function or activity of said peptide.

15. The method of claim 14, wherein said agent is administered to a host cell comprising an expression vector that expresses said peptide.

16. A method for identifying an agent that binds to any of the peptides of claim 2, said method comprising contacting the peptide with an agent and assaying the contacted mixture to determine whether a complex is formed with the agent bound to the peptide.

17. A pharmaceutical composition comprising an agent identified by the method of claim 16 and a pharmaceutically acceptable carrier therefor.

18. A method for treating a disease or condition mediated by a human kinase protein, said method comprising administering to a patient a pharmaceutically effective amount of an agent identified by the method of claim 16.

19. A method for identifying a modulator of the expression of a peptide of claim 2, said method comprising contacting a cell expressing said peptide with an agent, and determining if said agent has modulated the expression of said peptide.

20. An isolated human kinase peptide having an amino acid sequence that shares at least 70% homology with an amino acid sequence shown in SEQ ID NO:2.

21. A peptide according to claim 20 that shares at least 90 percent homology with an amino acid sequence shown in SEQ ID NO:2.

22. An isolated nucleic acid molecule encoding a human kinase peptide, said nucleic acid molecule sharing at least 80 percent homology with a nucleic acid molecule shown in SEQ ID NOS:1 or 3.

23. A nucleic acid molecule according to claim 22 that shares at least 90 percent homology with a nucleic acid molecule shown in SEQ ID NOS:1 or 3.

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   1  CAGCACGAGG AACTCCTTCT GATCACCTGG CCAGCTGAGG TCAGAGTGGG
  51  AGAGGCAGTG GTTCCATTGA AGGAGTACTC CTAACTGTCA GAAGCCTGGG
 101  CGGTCAGGAT GGGGTGCTGT CGCTTGGGCT GCGGGGGGTG TTCAGTTGCC
 151  CACAGTGTAT CTCAGGGTCT CACCAACCAT CCAAGCATGG TAGGCTGTGG
 201  CTGGCACCCA GGGTTGTGTG GCTGGGGAGG TGGTCTCCAC AGTTCCCTCC
 251  CTGCCCTCCC AGGGCCCCCA TCCATGCAGG TAACCATCGA GGATGTGCAG
 301  GCACAGACAG GCGGAACGGC CCAATTCGAG GCTATCATTG AGGGCGACCC
 351  ACAGCCCTCG GTGACCTGGT ACAAGGACAG CGTCCAGCTG GTGGACAGCA
 401  CCCGGCTTAG CCAGCAGCAA GAAGGCACCA CATACTCCCT GGTGCTGAGG
 451  CATGTGGCCT CGAAGGATGC CGGCGTTTAC ACCTGCCTGG CCCAAAACAC
 501  TGGTGGCCAG GTGCTCTGCA AGGCAGAGCT GCTGGTGCTT GGGGGGGACA
 551  ATGAGCCGGA CTCAGAGAAG CAAAGCCACC GGAGGAAGCT GCACTCCTTC
 601  TATGAGGTCA AGGAGGAGAT TGGAAGGGGC GTGTTTGGCT TCGTAAAAAG
 651  AGTGCAGCAC AAAGGAAACA AGATCTTGTG CGCTGCCAAG TTCATCCCCC
 701  TACGGAGCAG AACTCGGGCC CAGGCATACA GGGAGCGAGA CATCCTGGCC
 751  GCGCTGAGCC ACCCGCTGGT CACGGGGCTG CTGGACCAGT TTGAGACCCG
 801  CAAGACCCTC ATCCTCATCC TGGAGCTGTG CTCATCCGAG GAGCTGCTGG
 851  ACCGCCTGTA CAGGAAGGGC GTGGTGACGG AGGCCGAGGT CAAGGTCTAC
 901  ATCCAGCAGC TGGTGGAGGG GCTGCACTAC CTGCACAGCC ATGGCGTTCT
 951  CCACCTGGAC ATAAAGCCCT CTAACATCCT GATGGTGCAT CCTGCCCGGG
1001  AAGACATTAA AATCTGCGAC TTTGGCTTTG CCCAGAACAT CACCCCAGCA
1051  GAGCTGCAGT TCAGCCAGTA CGGCTCCCCT GAGTTCGTCT CCCCCGAGAT
1101  CATCCAGCAG AACCCTGTGA GCGAAGCCTC CGACATTTGG GCCATGGGTG
1151  TCATCTCCTA CCTCAGCCTG ACCTGCTCAT CCCCATTTGC CGGCGAGAGT
1201  GACCGTGCCA CCCTCCTGAA CGTCCTGGAG GGGCGCGTGT CATGGAGCAG
1251  CCCCATGGCT GCCCACCTCA GCGAAGACGC CAAAGACTTC ATCAAGGCTA
1301  CGCTGCAGAG AGCCCCTCAG GCCCGGCCTA GTGCGGCCCA GTGCCTCTCC
1351  CACCCCTGGT TCCTGAAATC CATGCCTGCG GAGGAGGCCC ACTTCATCAA
1401  CACCAAGCAG CTCAAGTTCC TCCTGGCCCG AAGTCGCTGG CAGCGTTCCC
1451  TGATGAGCTA CAAGTCCATC CTGGTGATGC GCTCCATCCC TGAGCTGCTG
1501  CGGGGCCCAC CCGACAGCCC CTCCCTCGGC GTAGCCCGGC ACCTCTGCAG
1551  GGACACTGGT GGCTCCTCCA GTTCCTCCTC CTCCTCTGAC AACGAGCTCG
1601  CCCCATTTGC CCGGGCTAAG TCACTGCCAC CCTCCCCGGT GACACACTCA
1651  CCACTGCTGC ACCCCCGGGG CTTCCTGCGG CCCTCGGCCA GCCTGCCTGA
1701  GGAAGCCGAG GCCAGTGAGC GCTCCACCGA GGCCCCAGCT CCGCCTGCAT
1751  CTCCCGAGGG TGCCGGGCCA CCGGCCGCCC AGGGCTGCGT GCCCCGGCAC
1801  AGCGTCATCC GCAGCCTGTT CTACCACCAG GCGGGTGAGA GCCCTGAGCA
1851  CGGGGCCCTG GCCCCGGGGA GCAGGCGGCA CCCGGCCCGG CGGCGGCACC
1901  TGCTGAAGGG CGGCTACATT GCGGGGGCGC TGCCAGGCCT GCGCGAGCCA
1951  CTGATGGAGC ACCGCGTGCT GGAGGAGGAG GCCGCCAGGG AGGAGCAGGC
2001  CACCCTCCTG GCCAAAGCCC CCTCATTCGA GACTGCCCTC CGGCTGCCTG
2051  CCTCTGGCAC CCACTTGGCC CCTGGCCACA GCCACTCCCT GGAACATGAC
2101  TCTCCGAGCA CCCCCCGCCC CTCCTCGGAG GCCTGCGGTG AGGCACAGCG
2151  ACTGCCTTCA GCCCCCTCCG GGGGGGCCCC TATCAGGGAC ATGGGGCACC
2201  CTCAGGGCTC CAAGCAGCTT CCATCCACTG GTGGCCACCC AGGCACTGCT
2251  CAGCCAGAGA GGCCATCCCC GGACAGCCCT TGGGGGCAGC CAGCCCCTTT
2301  CTGCCACCCC AAGCAGGGTT CTGCCCCCCA GGAGGGCTGC AGCCCCCACC
2351  CAGCAGTTGC CCCATGCCCT CCTGGCTCCT TCCCTCCAGG ATCTTGCAAA
2401  GAGGCCCCCT TAGTACCCTC AAGCCCCTTC TTGGGACAGC CCCAGGCACC
2451  CCCTGCCCCT GCCAAAGCAA GCCCCCCATT GGACTCTAAG ATGGGGCCTG
2501  GAGACATCTC TCTTCCTGGG AGGCCAAAAC CCGGCCCCTG CAGTTCCCCA
2551  GGGTCAGCCT CCCAGGCGAG CTCTTCCCAA GTGAGCTCCC TCAGGGTGGG
2601  CTCCTCCCAG GTGGGCACAG AGCCTGGCCC CTCCCTGGAT GCGGAGGGCT
2651  GGACCCAGGA GGCTGAGGAT CTGTCCGACT CCACACCCAC CTTGCAGCGG
2701  CCTCAGGAAC AGGTGACCAT GCGCAAGTTC TCCCTGGGTG GTCGCGGGGG
2751  CTACGCAGGC GTGGCTGGCT ATGGCACCTT TGCCTTTGGT GGAGATGCAG
2801  GGGGCATGCT GGGGCAGGGG CCCATGTGGG CCAGGATAGC CTGGGCTGTG
2851  TCCCAGTCGG AGGAGGAGGA GCAGGAGGAG GCCAGGGCTG AGTCCCAGTC
2901  GGAGGAGCAG CAGGAGGCCA GGGCTGAGAG CCCACTGCCC CAGGTCAGTG
2951  CAAGGCCTGT GCCTGAGGTC GGCAGGGCTC CCACCAGGAG CTCTCCAGAG
3001  CCCACCCCAT GGGAGGACAT CGGGCAGGTC TCCCTGGTGC AGATCCGGGA
3051  CCTGTCAGGT GATGCGGAGG CGGCCGACAC AATATCCCTG GACATTTCCG
3101  AGGTGGACCC CGCCTACCTC AACCTCTCAG ACCTGTACGA TATCAAGTAC
3151  CTCCCATTCG AGTTTATGAT CTTCAGGAAA GTCCCCAAGT CCGCTCAGCC
3201  AGAGCCGCCC TCCCCCATGG CTGAGGAGGA GCTGGCCGAG TTCCCGGAGC
3251  CCACGTGGCC CTGGCCAGGT GAACTGGGCC CCCACGCAGG CCTGGAGATC
3301  ACAGAGGAGT CAGAGGATGT GGACGCGCTG CTGGCAGAGG CTGCCGTGGG
3351  CAGGAAGCGC AAGTGGTCCT CGCCGTCACG CAGCCTCTTC CACTTCCCTG
3401  GGAGGCACCT GCCGCTGGAT GAGCCTGCAG AGCTGGGGCT GCGTGAGAGA
3451  GTGAAGGCCT CCGTGGAGCA CATCTCCCGG ATCCTGAAGG GCAGGCCGGA
3501  AGGTCTGGAG AAGGAGGGGC CCCCCAGGAA GAAGCCAGGC CTTGCTTCCT
3551  TCCGGCTCTC AGGTCTGAAG AGCTGGGACC GAGCGCCGAC ATTCCTAAGG
3601  GAGCTCTCAG ATGAGACTGT GGTCCTGGGC CAGTCAGTGA CACTGGCCTG
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FIGURE 1A

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3651  CCAGGTGTCA GCCCAGCCAG CTGCCCAGGC CACCTGGAGC AAAGACGGAG
3701  CCCCCCTGGA GAGCAGCAGC CGTGTCCTCA TCTCTGCCAC CCTCAAGAAC
3751  TTCCAGCTTC TGACCATCCT GGTGGTGGTG GCTGAGGACC TGGGTGTGTA
3801  CACCTGCAGC GTGAGCAATG CGCTGGGGAC AGTGACCACC ACGGGCGTCC
3851  TCCGGAAGGC AGAGCGCCCC TCATCTTCGC CATGCCCGGA TATCGGGGAG
3901  GTGTACGCGG ATGGGGTGCT GCTGGTCTGG AAGCCCGTGG AATCCTACGG
3951  CCCTGTGACC TACATTGTGC AGTGCAGCCT AGAAGGCGGC AGCTGGACCA
4001  CACTGGCCTC CGACATCTTT GACTGCTGCT ACCTGACCAG CAAGCTCTCC
4051  CGGGGTGGCA CCTACACCTT CCGCACGGCA TGTGTCAGCA AGGCAGGAAT
4101  GGGTCCCTAC AGCAGCCCCT CGGAGCAAGT CCTCCTGGGA GGGCCCAGCC
4151  ACCTGGCCTC TGAGGAGGAG AGCCAGGGGC GGTCAGCCCA ACCCCTGCCC
4201  AGCACAAAGA CCTTCGCATT CCAGACACAG ATCCAGAGGG GCCGCTTCAG
4251  CGTGGTGCGG CAATGCTGGG AGAAGGCCAG CGGGCGGGCG CTGGCCGCCA
4301  AGATCATCCC CTACCACCCC AAGGACAAGA CAGCAGTGCT GCGCGAATAC
4351  GAGGCCCTCA AGGGCCTGCG CCACCCGCAC CTGGCCCAGC TGCACGCAGC
4401  CTACCTCAGC CCCCGGCACC TGGTGCTCAT CTTGGAGCTG TGCTCTGGGC
4451  CCGAGCTGCT CCCCTGCCTG GCCGAGAGGG CCTCCTACTC AGAATCTGAG
4501  GTGAAGGACT ACCTGTGGCA GATGTTGAGT GCCACCCAGT ACCTGCACAA
4551  CCAGCACATC CTGCACCTGG ACCTGAGGTC CGAGAACATG ATCATCACCG
4601  AATACAACCT GCTCAAGGTC GTGGACCTGG GCAATGCACA GAGCCTCAGC
4651  CAGGAGAAGG TGCTGCCCTC AGACAAGTTC AAGGACTACC TAGAGACCAT
4701  GGCTCCAGAG CTCCTGGAGG GCCAGGGGGC TGTTCCACAG ACAGACATCT
4751  GGGCCATCGG TGTGACAGCC TTCATCATGC TGAGCGCCGA GTACCCGGTG
4801  AGCAGCGAGG GTGCACGCGA CCTGCAGAGA GGACTGCGCA AGGGGCTGGT
4851  CCGGCTGAGC CGCTGCTACG CGGGGCTGTC CGGGGGCGCC GTGGCCTTCC
4901  TGCGCAGCAC TCTGTGCGCC CAGCCCTGGG GCCGGCCCTG CGCGTCCAGC
4951  TGCCTGCAGT GCCCGTGGCT AACAGAGGAG GGCCCGGCCT GTTCGCGGCC
5001  CGCGCCCGTG ACCTTCCCTA CCGCGCGGCT GCGCGTCTTC GTGCGCAATC
5051  GCGAGAAGAG ACGCGCGCTG CTGTACAAGA GGCACAACCT GGCCCAGGTG
5101  CGCTGAGGGT CGCCCCGGCC ACACCCTTGG TCTCCCCGCT GGGGGTCGCT
5151  GCAGACGCGC CAATAAAAAC GCACAGCCGG GCGAGAAAAA AAAAAAAAAA
5201  AAAAAAA (SEQ ID NO:1)
```

FEATURES:
Start: 109
Stop: 5104

Homologous proteins:
Top BLAST Hits:

	Score	E
gi|7242949|dbj|BAA92535.1| (AB037718) KIAA1297 protein [Homo sa...	425	e-117
gi|8928460|sp|O75962|TRIO_HUMAN TRIPLE FUNCTIONAL DOMAIN PROTEI...	229	1e-58
gi|6005922|ref|NP_009049.1| triple functional domain (PTPRF int...	229	1e-58
gi|3024081|sp|Q15746|KMLS_HUMAN MYOSIN LIGHT CHAIN KINASE, SMOO...	206	2e-51
gi|90103|pir||A41674 myosin-light-chain kinase (EC 2.7.1.117), ...	205	4e-51
gi|7239696|gb|AAC18423.2| (U48959) myosin light chain kinase [H...	204	6e-51
gi|7239698|gb|AAD15921.2| (AF069601) myosin light chain kinase ...	204	6e-51
gi|1103677|emb|CAA62378.1| (X90870) myosin-light-chain kinase [...	204	6e-51
gi|3024085|sp|Q28824|KMLS_BOVIN MYOSIN LIGHT CHAIN KINASE, SMOO...	203	1e-50
gi|2851405|sp|P29294|KMLS_RABIT MYOSIN LIGHT CHAIN KINASE, SMOO...	203	1e-50
gi|3982821|gb|AAC83683.1| (AF081663) myosin light chain kinase ...	198	3e-49
gi|3982823|gb|AAC83684.1| (AF081664) myosin light chain kinase ...	198	3e-49
gi|3982827|gb|AAC83686.1| (AF081666) myosin light chain kinase ...	198	3e-49
gi|3982807|gb|AAC83676.1| (AF081656) myosin light chain kinase ...	198	3e-49

BLAST dbEST hit:

gi|7958129 /dataset=dbest /taxon=960...	1283	0.0

EXPRESSION INFORMATION FOR MODULATORY USE:
From BLAST dbEST hit:
gi|7958129 Human Colon carcinoma

From PCR-based tissue screening panels:
Human Placenta
Human Kidney
Human Lung
Human skeletal muscle
Human heart
Human fetal whole brain

FIGURE 1B

```
   1 MGCCRLGCGG CSVAHSVSQG LTNHPSMVGC GWHPGLCGWG GGLHSSLPAL
  51 PGPPSMQVTI EDVQAQTGGT AQFEAIIEGD PQPSVTWYKD SVQLVDSTRL
 101 SQQQEGTTYS LVLRHVASKD AGVYTCLAQN TGGQVLCKAE LLVLGGDNEP
 151 DSEKQSHRRK LHSFYEVKEE IGRGVFGFVK RVQHKGNKIL CAAKFIPLRS
 201 RTRAQAYRER DILAALSHPL VTGLLDQFET RKTLILILEL CSSEELLDRL
 251 YRKGVVTEAE VKVYIQQLVE GLHYLHSHGV LHLDIKPSNI LMVHPAREDI
 301 KICDFGFAQN ITPAELQFSQ YGSPEFVSPE IIQQNPVSEA SDIWAMGVIS
 351 YLSLTCSSPF AGESDRATLL NVLEGRVSWS SPMAAHLSED AKDFIKATLQ
 401 RAPQARPSAA QCLSHPWFLK SMPAEEAHFI NTKQLKFLLA RSRWQRSLMS
 451 YKSILVMRSI PELLRGPPDS PSLGVARHLC RDTGGSSSSS SSSDNELAPF
 501 ARAKSLPPSP VTHSPLLHPR GFLRPSASLP EEAEASERST EAPAPPASPE
 551 GAGPPAAQGC VPRHSVIRSL FYHQAGESPE HGALAPGSRR HPARRRHLLK
 601 GGYIAGALPG LREPLMEHRV LEEEAAREEQ ATLLAKAPSF ETALRLPASG
 651 THLAPGHSHS LEHDSPSTPR PSSEACGEAQ RLPSAPSGGA PIRDMGHPQG
 701 SKQLPSTGGH PGTAQPERPS PDSPWGQPAP FCHPKQGSAP QEGCSPHPAV
 751 APCPPGSFPP GSCKEAPLVP SSPFLGQPQA PPAPAKASPP LDSKMGPGDI
 801 SLPGRPKPGP CSSPGSASQA SSSQVSSLRV GSSQVGTEPG PSLDAEGWTQ
 851 EAEDLSDSTP TLQRPQEQVT MRKFSLGGRG GYAGVAGYGT FAFGGDAGGM
 901 LGQGPMWARI AWAVSQSEEE EQEEARAESQ SEEQQEARAE SPLPQVSARP
 951 VPEVGRAPTR SSPEPTPWED IGQVSLVQIR DLSGDAEAAD TISLDISEVD
1001 PAYLNLSDLY DIKYLPFEFM IFRKVPKSAQ PEPPSPMAEE ELAEFPEPTW
1051 PWPGELGPHA GLEITEESED VDALLAEAAV GRKRKWSSPS RSLFHFPGRH
1101 LPLDEPAELG LRERVKASVE HISRILKGRP EGLEKEGPPR KKPGLASFRL
1151 SGLKSWDRAP TFLRELSDET VVLGQSVTLA CQVSAQPAAQ ATWSKDGAPL
1201 ESSSRVLISA TLKNFQLLTI LVVVAEDLGV YTCSVSNALG TVTTTGVLRK
1251 AERPSSSPCP DIGEVYADGV LLVWKPVESY GPVTYIVQCS LEGGSWTTLA
1301 SDIFDCCYLT SKLSRGGTYT FRTACVSKAG MGPYSSPSEQ VLLGGPSHLA
1351 SEEESQGRSA QPLPSTKTFA FQTQIQRGRF SVVRQCWEKA SGRALAAKII
1401 PYHPKDKTAV LREYEALKGL RHPHLAQLHA AYLSPRHLVL ILELCSGPEL
1451 LPCLAERASY SESEVKDYLW QMLSATQYLH NQHILHLDLR SENMIITEYN
1501 LLKVVDLGNA QSLSQEKVLP SDKFKDYLET MAPELLEGQG AVPQTDIWAI
1551 GVTAFIMLSA EYPVSSEGAR DLQRGLRKGL VRLSRCYAGL SGGAVAFLRS
1601 TLCAQPWGRP CASSCLQCPW LTEEGPACSR PAPVTFPTAR LRVFVRNREK
1651 RRALLYKRHN LAQVR  (SEQ ID NO:2)
```

FEATURES:
Functional domains and key regions:
Prosite results:
[1] PDOC00001 PS00001 **ASN_GLYCOSYLATION**
N-glycosylation site

1005-1008 NLSD

---

[2] PDOC00004 PS00004 **CAMP_PHOSPHO_SITE**
cAMP- and cGMP-dependent protein kinase phosphorylation site

Number of matches: 2

1	872-875	RKFS
2	1084-1087	RKWS

---

[3] PDOC00005 PS00005 **PKC_PHOSPHO_SITE**
Protein kinase C phosphorylation site

Number of matches: 23

1	97-99	STR
2	152-154	SEK
3	156-158	SHR
4	230-232	TRK
5	364-366	SDR
6	450-452	SYK
7	536-538	SER
8	588-590	SRR
9	668-670	TPR
10	762-764	SCK
11	827-829	SLR
12	870-872	TMR
13	947-949	SAR
14	1147-1149	SFR
15	1203-1205	SSR
16	1211-1213	TLK
17	1310-1312	TSK
18	1320-1322	TFR

FIGURE 2A

19	1365-1367	STK
20	1391-1393	SGR
21	1434-1436	SPR
22	1521-1523	SDK
23	1638-1640	TAR

[4] PDOC00006 PS00006 CK2_PHOSPHO_SITE
Casein kinase II phosphorylation site

Number of matches: 21

1	59-62	TIED
2	163-166	SFYE
3	242-245	SSEE
4	257-260	TEAE
5	312-315	TPAE
6	459-462	SIPE
7	491-494	SSSD
8	493-496	SDNE
9	528-531	SLPE
10	762-765	SCKE
11	915-918	SQSE
12	929-932	SQSE
13	917-920	SEEE
14	1351-1354	SEEE
15	915-918	SQSE
16	929-932	SQSE
17	961-964	SSPE
18	966-969	TPWE
19	997-1000	SEVD
20	1336-1339	SPSE
21	917-920	SEEE

[5] PDOC00008 PS00008 MYRISTYL
N-myristoylation site

Number of matches: 27

1	7-12	GCGGCS
2	10-15	GCSVAH
3	41-46	GGLHSS
4	42-47	GLHSSL
5	106-111	GTTYSL
6	122-127	GVYTCL
7	133-138	GQVLCK
8	484-489	GGSSSS
9	485-490	GSSSSS
10	601-606	GGYIAG
11	606-611	GALPGL
12	708-713	GGHPGT
13	877-882	GGRGGY
14	880-885	GGYAGV
15	894-899	GGDAGG
16	898-903	GGMLGQ
17	1061-1066	GLEITE
18	1174-1179	GQSVTL
19	1229-1234	GVYTCS
20	1240-1245	GTVTTT
21	1293-1298	GGSWTT
22	1294-1299	GSWTTL
23	1316-1321	GGTYTF
24	1508-1513	GNAQSL
25	1575-1580	GLRKGL
26	1589-1594	GLSGGA
27	1592-1597	GGAVAF

FIGURE 2B

[6] PDOC00009 PS00009 AMIDATION
Amidation site

1080-1083 VGRK

---

[7] PDOC00373 PS00343 GRAM_POS_ANCHORING
Gram-positive cocci surface proteins 'anchoring' hexapeptide

704-709 LPSTGG

---

[8] PDOC00100 PS00107 PROTEIN_KINASE_ATP
Protein kinases ATP-binding region signature

171-194 IGRGVFGFVKRVQHKGNKILCAAK

---

[9] PDOC00100 PS00108 PROTEIN_KINASE_ST
Serine/Threonine protein kinases active-site signature

280-292 VLHLDIKPSNILM

---

[10] PDOC00100 PS00109 PROTEIN_KINASE_TYR
Tyrosine protein kinases specific active-site signature

1484-1496 ILHLDLRSENMII

---

[11] PDOC00565 PS00659 GLYCOSYL_HYDROL_F5
Glycosyl hydrolases family 5 signature

142-151 LVLGGDNEPD

FIGURE 2C

BLAST Alignment to Top Hits:

>gi|7242949|dbj|BAA92535.1| (AB037718) KIAA1297 protein [Homo sapiens]
Length = 2242

Score = 425 bits (1081), Expect = e-117
Identities = 305/876 (34%), Positives = 423/876 (47%), Gaps = 106/876 (12%)

```
Query: 54   PSMQVTIEDVQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLVDSTRLSQQQEGTTYSLVL 113
            P  +  +EDV+   G TA+F  ++EG P P + WYKD V L +S+ +S   E   SLV+
Sbjct: 504  PRFESIMEDVEVGAGETARFAVVVEGKPLPDIMWYKDEVLLTESSHVSFVYEENECSLVV 563

Query: 114  RHVASKDAGVYTCLAQNTGGQVLCKAELLVLGGDN----EPDSEKQSHR-RKLHSFYEVK 168
                ++D GVYTC AQN  G+V CKAEL V          E   E + HR R+L  FY++
Sbjct: 564  LSTGAQDGGVYTCTAQNLAGEVSCKAELAVHSAQTAMEVEGVGEDEDHRGRRLSDFYDIH 623

Query: 169  EEIGRGVFGFVKRVQHKGNKILCAAKFIPLRSRTRAQAYRERDILAALSHPLVTGLLDQF 228
            +EIGRG F +++R+  + + +  AAKFIP +++ +A A RE  +LA L H  V    + F
Sbjct: 624  QEIGRGAFSYLRRIVERSSGLEFAAKFIPSQAKPKASARREARLLARLQHDCVLYFHEAF 683

Query: 229  ETRKTLILILELCSSEELLDRLYRKGVVTEAEVKVYIQQLVEGLHYLHSHGVLHLDIKPS 288
            E R+ L+++ ELC+ EELL+R+ RK  V E+E++ Y++Q++EG+HYLH    VLHLD+KP
Sbjct: 684  ERRRGLVIVTELCT-EELLERIARKPTVCESEIRAYMRQVLEGIHYLHQSHVLHLDVKPE 742

Query: 289  NILMVHPA--REDIKICDFGFAQNITPAELQFSQYGSPEFVSPEIIQQNPVSEASDIWAM 346
            N+L+   A    + ++ICDFG AQ +TP E Q+ QYG+PEFV+PEI+ Q+PVS  +DIW +
Sbjct: 743  NLLVWDGAAGEQQVRICDFGNAQELTPGEPQYCQYGTPEFVAPEIVNQSPVSGVTDIWPV 802

Query: 347  GVISYLSLTCSSPFAGESDRATLLNVLEGRVSWSSPMAAHLSEDAKDF-IKATLQRAPQA 405
            GV+++L LT  SPF GE+DR TL+N+    V++       LS +A+ F IK  +Q   +
Sbjct: 803  GVVAFLCLTGISPFVGENDRTTLMNIRNYNVAFEETTFLSLSREARGFLIKVLVQ--DRL 860

Query: 406  RPSAAQCLSHPWFLKSMPAEEAHFINTKQLKFLLARSRWQRSLMSYKSILVMRSIPELLR 465
            RP+A + L HPWF       E   ++T  LK  L+R RWQRS +SYK  LV+R IPELLR
Sbjct: 861  RPTAEETLEHPWFKTQAKGAE---VSTDHLKLFLSRRRWQRSQISYKCHLVLRPIPELLR 917

Query: 466  GPPDSPSLGVARHLCRDTGGSSSSSSSSDNELAPFARAK----------SLPPSPVTH 513
              PP+   + + R      +GG SSSS S + EL                SL   P
Sbjct: 918  APPERVWVTMPRR-PPPSGGLSSSSDSEEEELEELPSVPRPLQPEFSGSRVSLTDIPTED 976

Query: 514  SPLLHPRGFLRPSASLPEEAEASERSTEAPAPPASPEGAGPPAAQGCVPRHSVI------ 567
              L  P          E+  A  +  EAP+P A P     PAA G  PR   +
Sbjct: 977  EALGTPETGAATPMDWQEQGRAPSQDQEAPSPEALPSPGQEPAA-GASPRRGELRRGSSA 1035

Query: 568  -------------RSLFYHQAGESPEHGALAPG--------------SRRHPARRRHLLK 600
                      R L    + E P+  +  PG                ++R  A R+ LL+
Sbjct: 1036 ESALPRAGPRELGRGLHKAASVELPQRRSPGPGATRLARGGLGEGEYAQRLQALRQRLLR 1095

Query: 601  GGYIAGALPGLREPLMEH----------RVLEEEAAREEQATL----LAKAPSFETALR 645
            GG   G + GLR PL+E            R    EAA   Q  L    L K+ SF
Sbjct: 1096 GGPEDGKVSGLRGPLLESLGGRARDPRMARAASSEAAPHHQPPLENRGLQKSSSFSQGEA 1155

Query: 646  LPASGTHLAPGHSHSLEHDSPSTPR----PSSEACGEAQRLPSAPSGGAPIRDMGHPQGS 701
              P  G H   G    +        R    PS  A  EAQ  PS+P+          P
Sbjct: 1156 EP-RGRHRRAGAPLEIPVARLGARRLQESPSLSALSEAQ--PSSPA---------RPSAP 1203

Query: 702  KQLPSTGGHPGTAQPERPSPDSPWGQPAPFCHPKQGSAPQEGCSPHPAVAPCPP----GS 757
            K  PST   P +A+P   +P      PAP   P Q  AP+    P  A  P PP     +
Sbjct: 1204 K--PST---PKSAEPSATTPSDAPQPPAP--QPAQDKAPEPRPEPVRASKPAPPPQALQT 1256

Query: 758  FPPGSCKEAPLVPSSPFLGQPQAPPAPAKASPPLDSKMGPGDISLPGRPKPGPCSSPGSA 817
                  A ++ S    G  Q  P+   A+PP + K       +    P PG  +
Sbjct: 1257 LALPLTPYAQIIQSLQLSGHAQG-PSQGPAAPPSEPKPHAAVFARVASPPPG--APEKRV 1313

Query: 818  SQASSSQVSSLRVGSSQVGTEPGPSLDAEGWTQEAE 853
              A    V + +     V   PG SL +     E+E
Sbjct: 1314 PSAGGPPVLAEKARVPTVPPRPGSSLSSSIENLESE 1349  (SEQ ID NO:4)
```

FIGURE 2D

```
 Score =  210 bits (529), Expect = 1e-52
 Identities = 111/281 (39%), Positives = 156/281 (55%), Gaps = 2/281 (0%)

Query: 1336 SPSEQVLLGGPSHLASEEESQGRSAQPLPSTKTFAFQTQIQRGRFSVVRQCWEKASGRAL 1395
          SP+++V+    S   S    +G + +  P  K + F  +  RGRF VVR C E A+GR
Sbjct: 1952 SPAKEVVSSPGSSPRSSPRPEGTTLRQGPPQKPYTFLEEKARGRFGVVRACRENATGRTF 2011

Query: 1396 AAKIIPYHPKDKTAVLREYEALKGLRHPHLAQLHAAYLSPRHLVLILELCSGPELLPCLA 1455
           AKI+PY  + K  VL+EYE L+ L H  +  LH AY++PR+LVLI E C   ELL  L+
Sbjct: 2012 VAKIVPYAAEGKPRVLQEYEVLRTLHHERIMSLHEAYITPRYLVLIAESCGNRELLCGLS 2071

Query: 1456 ERASYSESEVKDYLWQMLSATQYLHNQHILHLDLRSENMIITEYNLLKVVDLGNAQSLSQ 1515
          +R  YSE +V  Y+ Q+L    YLH  H+LHLD++ +N+++   N LK+VD G+AQ  +
Sbjct: 2072 DRFRYSEDDVATYMVQLLQGLDYLHGHHVLHLDIKPDNLLLAPDNALKIVDFGSAQPYNP 2131

Query: 1516 EKVLPSDKFKDYLETMAPELLEGQGAVPQTDIWAIGVTAFIMLSAEYPVSSEGARDLQRG 1575
          + + P       LE MAPE+++G+     TDIW  GV  +IMLS   P      ++ +
Sbjct: 2132 QALRPLGHRTGTLEFMAPEMVKGEPIGSATDIWGAGVLTYIMLSGRSPFYEPDPQETEAR 2191

Query: 1576 LRKGLVRLSRCYAGLSGGAVAFLRSTLCAQPWGRPCASSCL 1616
          +  G     + Y   S  A  FLR  L   PW RP  SSCL
Sbjct: 2192 IVGGRFDAFQLYPNTSQSATLFLRKVLSVHPWSRP--SSCL 2230 (SEQ ID NO:5)


 Score =  170 bits (426), Expect = 1e-40
 Identities = 168/574 (29%), Positives = 256/574 (44%), Gaps = 42/574 (7%)

Query: 1103 LDEP--AELGLRERVKASVEHISRILKGRPEGLEKEGPPRKKPGLASFRLSGLKSWDRAP 1160
          L EP  A  GLR+      V+HI R+L    +   K  PP +   L    L    + + AP
Sbjct: 358  LREPGWAATGLRK----GVQHIFRVLSTTVKSSSKPSPPSEPVQL----LEHGPTLEEAP 409

Query: 1161 TFLRELSDETVVLGQSVTLACQVSAQPAAQATW-SKDGAPLESSSRVL-ISATLKNFQLL 1218
            L +      VV GQ  ++     +     AQ  W S  GA LE+ + V  +S     +  L
Sbjct: 410  AMLDKPDIVYVVEGQPASVTVTFN-HVEAQVVWRSCRGALLEARAGVYELSQPDDDQYCL 468

Query: 1219 TILVVVAEDLGVYTCSVSNALGTVTTTGVLRKAERPS-SSPCPDI----GEVYADGVLLV 1273
          T  I  V   D+G  TC+  N  GT T +  L  AE P   S   D+     GE      V++
Sbjct: 469  RICRVSRRDMGALTCTARNRHGTQTCSVTLELAEAPRFESIMEDVEVGAGETARFAVVVE 528

Query: 1274 WKPVESYGPVTYIVQCSLEGGSWTTLASDIFDCCY--LTSKLSRGGTYTFRTACVSKAGM 1331
           KP+     + Y  +  L   S  +   +  +C    L++    GG YT     C ++
Sbjct: 529  GKPLPDI--MWYKDEVLLTESSHVSFVYEENECSLVVLSTGAQDGGVYT----CTAQNLA 582

Query: 1332 GPYSSPSEQVLLGGPSHLASEEESQGRSAQPLPSTKTFAFQTQIQRGRFSVVRQCWEKAS 1391
          G  S  +E  +    + +  E   +    +    + +  +I RG FS +R+  E++S
Sbjct: 583  GEVSCKAELAVHSAQTAMEVEGVGEDEDHRGRRLSDFYDIHQEIGRGAFSYLRRIVERSS 642

Query: 1392 GRALAAKIIPYHPKDKTAVLREYEALKGLRHPHLAQLHAAYLSPRHLVLILELCSGPELL 1451
          G   AAK IP   K K +  RE   L  L+H  +   H A+   R LV++ ELC+  ELL
Sbjct: 643  GLEFAAKFIPSQAKPKASARREARLLARLQHDCVLYFHEAFERRRGLVIVTELCT-EELL 701

Query: 1452 PCLAERASYSESEVKDYLWQMLSATQYLHNQHILHLDLRSENMIITE----YNLLKVVDL 1507
           +A + +  ESE++ Y+ Q+L    YLH  H+LHLD++ +N+++ +        +++ D
Sbjct: 702  ERIARKPTVCESEIRAYMRQVLEGIHYLHQSHVLHLDVKPENLLVWDGAAGEQQVRICDF 761

Query: 1508 GNAQSLSQEKVLPSDKFKDYLETMAPELLEGQGAVPQTDIWAIGVTAFIMLSAEYPVSSE 1567
          GNAQ L+  +  P       E +APE++       TDIW +GV AF+ L+   P   E
Sbjct: 762  GNAQELTPGE--PQYCQYGTPEFVAPEIVNQSPVSGVTDIWPVGVVAFLCLTGISPFVGE 819

Query: 1568 GARDLQRGLRKGLVRLSR-CYAGLSGGAVAFLRSTLCAQPWGRPCASSCLQCPWLTEEGP 1626
            R     +R   V      + LS  A  FL   L  Q   RP A   L+ PW   +
Sbjct: 820  NDRTTLMNIRNYNVAFEETTFLSLSREARGFLIKVL-VQDRLRPTAEETLEHPWFKTQ-- 876

Query: 1627 ACSRPAPVTFPTARLRVFV-RNREKRRALLYKRH 1659
            ++ A V+  T  L++F+ R R +R  + YK H
Sbjct: 877  --AKGAEVS--TDHLKLFLSRRRWQRSQISYKCH 906  (SEQ ID NO:6)
```

FIGURE 2E

```
 Score =  145 bits (362), Expect = 4e-33
 Identities = 85/253 (33%), Positives = 135/253 (52%), Gaps = 5/253 (1%)

Query: 165  YEVKEEIGRGVFGFVKRVQHKGNKILCAAKFIPLRSRTRAQAYRERDILAALSHPLVTGL 224
            Y   EE  RG FG V+  +          AK +P  +  + +  +E ++L  L H  +  L
Sbjct: 1985 YTFLEEKARGRFGVVRACRENATGRTFVAKIVPYAAEGKPRVLQEYEVLRTLHHERIMSL 2044

Query: 225  LDQFETRKTLILILELCSSEELLDRLYRKGVVTEAEVKVYIQQLVEGLHYLHSHGVLHLD 284
             + + T + L+LI E C + ELL  L  +   +E +V  Y+ QL++GL YLH H VLHLD
Sbjct: 2045 HEAYITPRYLVLIAESCGNRELLCGLSDRFRYSEDDVATYMVQLLQGLDYLHGHHVLHLD 2104

Query: 285  IKPSNILMVHPAREDIKICDFGFAQNITPAELQ--FSQYGSPEFVSPEIIQQNPVSEASD 342
            IKP N+L+       +KI DFG AQ   P  L+    + G+ EF++PE+++  P+  A+D
Sbjct: 2105 IKPDNLLLA--PDNALKIVDFGSAQPYNPQALRPLGHRTGTLEFMAPEMVKGEPIGSATD 2162

Query: 343  IWAMGVISYLSLTCSSPFAGESDRATLLNVLEGRVSWSSPMAAHLSEDAKDFIKATLQRA 402
            IW  GV++Y+ L+  SPF     + T   ++ GR   +  +  + S+ A  F++  L
Sbjct: 2163 IWGAGVLTYIMLSGRSPFYEPDPQETEARIVGGRFD-AFQLYPNTSQSATLFLRKVLSVH 2221

Query: 403  PQARPSAAQCLSH 415
            P +RPS+   + H
Sbjct: 2222 PWSRPSSCLSVCH 2234  (SEQ ID NO:7)


 Score =  128 bits (319), Expect = 4e-28
 Identities = 81/245 (33%), Positives = 120/245 (48%), Gaps = 19/245 (7%)

Query: 1139 PRKKPGLASFRLSGL----------KSWDRAPTFLRELSDETVVLGQSVTLACQVSAQP 1187
            PRK  GL+  LS               D  P F  +L D+ ++ G++ TL C  +A P
Sbjct: 1571 PRKDKGLSPPNLSASVQEELGHQYVRSESDFPPVFHIKLKDQVLLEGEAATLLCLPAACP 1630

Query: 1188 AAQATWSKDGAPLESSSRVLISATLKNFQLLTILVVVAEDLGVYTCSVSNALGTVTTTGV 1247
            A   +W KD   L S   V+I +     QLL+I        G+Y CS +N LG++T++
Sbjct: 1631 APHISWMKDKKSLRSEPSVIIVSCKDGRQLLSIPRAGKRHAGLYECSATNVLGSITSSCT 1690

Query: 1248 LRKAERPSSSPCPDIGEVYADGVLLVWKPVESYGPVTYIVQCSLEGGS-WTTLASDIFDC 1306
            +  A  P     P++ + Y D  L++WKP +S  P TY ++  ++G S W  ++S I DC
Sbjct: 1691 VAVARVPGKLAPPEVTQTYQDTALVLWKPGDSRAPCTYTLERRVDGESVWHPVSSGIPDC 1750

Query: 1307 CYLTSKLSRGGTYTFRTACVSKAGMGPYSSPSEQVLLGG-------PSHLASEEESQGRS 1359
             Y  + L  G T  FR AC ++AG GP+S+ SE+V + G       PS    E     R
Sbjct: 1751 YYNVTHLPVGVTVRFRVACANRAGQGPFSNSSEKVFVRGTQDSSAVPSAAHQEAPVTSRP 1810

Query: 1360 AQPLP 1364
            A+  P
Sbjct: 1811 ARARP 1815  (SEQ ID NO:8)


 Score = 71.0 bits (171), Expect = 9e-11
 Identities = 41/115 (35%), Positives = 57/115 (48%), Gaps = 4/115 (3%)

Query: 60   IEDVQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLVDSTRLSQQQEGTTYSLVLRHVASK 119
            +EDV+   G  A+F+  I G P P VTW      + +S  L  +Q+G  +SL + HV S+
Sbjct: 89   LEDVEVLEGRAARFDCKISGTPPPVVTWTHFGCPMEESENLRLRQDGGLHSLHIAHVGSE 148

Query: 120  DAGVYTCLAQNTGGQVLCKAELLVLGGDNEPDSEKQSHRRKLHSFYEVKEEIGRG 174
            D G+Y   A NT GQ  C A+L V     EP +        KL     + EE  +G
Sbjct: 149  DEGLYAVSAVNTHGQAHCSAQLYV----EEPRTAASGPSSKLEKMPSIPEEPEQG 199  (SEQ ID NO:9)


 Score = 60.1 bits (143), Expect = 2e-07
 Identities = 54/199 (27%), Positives = 81/199 (40%), Gaps = 12/199 (6%)

Query: 1160 PTFLRELSDETVVLGQSVTLACQVSAQPAAQATWSKDGAPLESSSRVLISATLKNFQLLT 1219
            P FLR L D  V L +   L CQV+  P    +W  +G  ++SS     ++   ++   L
Sbjct: 207  PDFLRPLQDLEVGLAKEAMLECQVTGLPYPTISWFHNGHRIQSSDDRRMT-QYRDVHRLV 265

Query: 1220 ILVVVAEDLGVYTCSVSNALGTVTTTGVLRRAERPSSSP--CPDIGEVYADGVLLVWKPV 1277
               V  +  GVY   ++N LG       L  +     P   P +  V    V L W P
Sbjct: 266  FPAVGPQHAGVYKSVIANKLGKAACYAHLYVTDVVPGPPDGAPQVVAVTGRMVTLTWNPP 325

Query: 1278 ESY------GPVTYIVQCSLEGG-SWTTLASDIFDCCYLTSKLSRGGTYTFRTACVSKAG 1330
```

FIGURE 2F

```
            S         +TY VQ  + G   WT L + + +  +  + L +G  + FR    +
Sbjct: 326  RSLDMAIDPDSLTYTVQHQVLGSDQWTALVTGLREPGWAATGLRKGVQHIFRVLSTTVKS 385

Query: 1331 MGPYSSPSE--QVLLGGPS 1347
               S PSE  Q+L  GP+
Sbjct: 386  SSKPSPPSEPVQLLEHGPT 404  (SEQ ID NO:10)


 Score = 45.7 bits (106), Expect = 0.004
 Identities = 30/102 (29%), Positives = 45/102 (43%), Gaps = 1/102 (0%)

Query: 1159 APTFLRELSDETVVLGQSVTLACQVSAQPAAQATWSKDGAPLESSSRVLISATLKNFQLL 1218
          AP F R L D  V+ G++    C++S  P    TW+  G P+E S  + +         L
Sbjct: 82   APLFTRLLEDVEVLEGRAARFDCKISGTPPPVVTWTHFGCPMEESENLRLRQD-GGLHSL 140

Query: 1219 TILVVVAEDLGVYTCSVSNALGTVTTTGVLRKAERPSSSPCP 1260
           I  V +ED G+Y  S  N  G    +  L   E  +++  P
Sbjct: 141  HIAHVGSEDEGLYAVSAVNTHGQAHCSAQLYVEEPRTAASGP 182  (SEQ ID NO:11)


 Score = 43.8 bits (101), Expect = 0.015
 Identities = 58/217 (26%), Positives = 84/217 (37%), Gaps = 23/217 (10%)

Query: 619  RVLEEEAAREEQATLLAKAPSFETALRLPASGTHLAPGHSHSLEHDSPSTPRPSSEACGE 678
          R  ++ +A    A   A   S     R P S T LAP  + +       T  PSS
Sbjct: 1788 RGTQDSSAVPSAAHQEAPVTSRPARARPPDSPTSLAPPLAPAAPTPPSVTVSPSSPPTPP 1847

Query: 679  AQRLPSAPSGGAPIRDMGHPQGSKQLPSTGGHPGTAQPERPSPDSPWGQPAPFCHPKQGS 738
          +Q L S  + G P +    P+  + L +       A+P  PS      +P PF
Sbjct: 1848 SQALSSLKAVGPPPQTP--PRRHRGLQAAR----PAEPTLPSTHVTPSEPKPFVLD---- 1897

Query: 739  APQEGCSPHPAVAPCPPGSFPPGSCKEAPLVPSSPFLGQPQAPPAPAKASPPLDSKMGPG 798
               +  P  A  P G  P  S    P+   + F+  P AP  PA   PP  +K+
Sbjct: 1898 ------TGTPIPASTPQGVKPVSS--STPVYVVTSFVSAPPAPEPPAPEPPPEPTKVTVQ 1949

Query: 799  DISLPGRPKPGPCSSPGSASQAS-SSQVSSLRVGSSQ 834
           +S    P     SSPGS+ ++S   + ++LR G  Q
Sbjct: 1950 SLS----PAKEVVSSPGSSPRSSPRPEGTTLRQGPPQ 1982  (SEQ ID NO:12)


 Score = 43.0 bits (99), Expect = 0.026
 Identities = 25/92 (27%), Positives = 44/92 (47%), Gaps = 4/92 (4%)

Query: 54   PSMQVTIEDVQAQTGGTAQFEAIIEGDPQPSVTWYKDS--VQLVDSTRLSQQQEGTTYSL 111
          P     ++D++      A  E  + G P P+++W+ +   +Q  D  R++Q ++    + L
Sbjct: 207  PDFLRPLQDLEVGLAKEAMLECQVTGLPYPTISWFHNGHRIQSSDDRRMTQYRD--VHRL 264

Query: 112  VLRHVASKDAGVYTCLAQNTGGQVLCKAELLV 143
          V  V  + AGVY  +  N  G+  C A L V
Sbjct: 265  VFPAVGPQHAGVYKSVIANKLGKAACYAHLYV 296  (SEQ ID NO:13)


>gi|8928460|sp|O75962|TRIO_HUMAN TRIPLE FUNCTIONAL DOMAIN PROTEIN
           (PTPRF INTERACTING PROTEIN) >gi|3644048|gb|AAC43042.1|
           (AF091395) Trio isoform [Homo sapiens]
           Length = 3038

 Score =  229 bits (579), Expect = 1e-58
 Identities = 143/418 (34%), Positives = 215/418 (51%), Gaps = 11/418 (2%)

Query: 53   PPSMQVTIEDVQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLVDST---RLSQQQEGTTY 109
          PP   + + +V  +TG T      + G P+ S+TW       +S    G
Sbjct: 2625 PPEFVIPLSEVTCETGETVVLRCRVCGRPKASITWKGPEHNTLNNDGHYSISYSDLGEA- 2683

Query: 110  SLVLRHVASKDAGVYTCLAQNTGGQVLCKAELLVLGGDNEPDSEKQSHRRKLHSFYEVKE 169
          +L +  V ++D G+YTC+A N  G     A L VLG     D    + +    SFY
Sbjct: 2684 TLKIVGVTTEDDGIYTCIAVNDMGSASSSASLRVLGPGM--DGIMVTWKDNFDSFYSEVA 2741
```

FIGURE 2G

```
Query: 170  EIGRGVFGFVKRVQHKGNKILCAAKFIPLRSRTRAQAYRERDILAALSHPLVTGLLDQFE 229
            E+GRG F  VK+   KG K   A KF+  +   R Q   E  IL +L HPL+ GLLD FE
Sbjct: 2742 ELGRGRFSVVKKCDQKGTKRAVATKFVNKKLMKRDQVTHELGILQSLQHPLLVGLLDTFE 2801

Query: 230  TRKTLILILELCSSEELLDRLYRKGVVTEAEVKVYIQQLVEGLHYLHSHGVLHLDIKPSN 289
            T  + IL+LE+     LLD + R G +TE +++ ++ +++E + YLH+  + HLD+KP N
Sbjct: 2802 TPTSYILVLEMADQGRLLDCVVRWGSLTEGKIRAHLGEVLEAVRYLHNCRIAHLDLKPEN 2861

Query: 290  ILMVHP-AREDIKICDFGFAQNITPAELQFSQYGSPEFVSPEIIQQNPVSEASDIWAMGV 348
            IL+    A+  IK+ DFG A  +          G+PEF +PEII  NPVS  SD W++GV
Sbjct: 2862 ILVDESLAKPTIKLADFGDAVQLNTTYYIHQLLGNPEFAAPEIILGNPVSLTSDTWSVGV 2921

Query: 349  ISYLSLTCSSPFAGESDRATLLNVLEGRVSWSSPMAAHLSEDAKDFIKATLQRAPQARPS 408
            ++Y+ L+  SPF  +S   T LN+     S+       +S+ AK+F+   LQ  P  RPS
Sbjct: 2922 LTYVLLSGVSPFLDDSVEETCLNICRLDFSFPDDYFKGVSQKAKEFVCFLLQEDPAKRPS 2981

Query: 409  AAQCLSHPWFLKSMPAEEAHFINTKQLKFLLARSRWQ---RSLMSYKSILVMRSIPEL 463
            AA  L   W L++         ++T +L   + R + Q   R + S K+ L  R +P +
Sbjct: 2982 AALALQEQW-LQAGNGRSTGVLDTSRLTSFIERRKHQNDVRPIRSIKNFLQSRLLPRV 3038
(SEQ ID NO:14)

 Score =  121 bits (300), Expect = 7e-26
 Identities = 82/280 (29%), Positives = 137/280 (48%), Gaps = 10/280 (3%)

Query: 1374 QIQRGRFSVVRQCWEKASGRALAAKIIPYHPKDKTAVLREYEALKGLRHPHLAQLHAAYL 1433
            ++ RGRFSVV++C +K + RA+A K +      +  V  E   L+ L+HP L  L   +
Sbjct: 2742 ELGRGRFSVVKKCDQKGTKRAVATKFVNKKLMKRDQVTHELGILQSLQHPLLVGLLDTFE 2801

Query: 1434 SPRHLVLILELCSGPELLPCLAERASYSESEVKDYLWQMLSATQYLHNQHILHLDLRSEN 1493
            +P   +L+LE+     LL C+    S +E +++ +L ++L A +YLHN  I HLDL+ EN
Sbjct: 2802 TPTSYILVLEMADQGRLLDCVVRWGSLTEGKIRAHLGEVLEAVRYLHNCRIAHLDLKPEN 2861

Query: 1494 MIITE---YNLLKVVDLGNAQSLSQEKVLPSDKFKDYLETMAPELLEGQGAVPQTDIWAI 1550
            +++ E      +K+ D G+A  L+    +   +    E  APE++ G       +D W++
Sbjct: 2862 ILVDESLAKPTIKLADFGDAVQLNTTYYI--HQLLGNPEFAAPEIILGNPVSLTSDTWSV 2919

Query: 1551 GVTAFIMLSAEYPVSSEGARDLQRGL-RKGLVRLSRCYAGLSGGAVAFLRSTLCAQPWGR 1609
            GV  ++LS   P   +   + R        + G+S  A  F+   L   P R
Sbjct: 2920 GVLTYVLLSGVSPFLDDSVEETCLNICRLDFSFPDDYFKGVSQKAKEFVCFLLQEDPAKR 2979

Query: 1610 PCASSCLQCPWLTEEGPACSRPAPVTFPTARLRVFVRNRE 1649
            P A+  LQ  WL     A +  +     T+RL  F+  R+
Sbjct: 2980 PSAALALQEQWL----QAGNGRSTGVLDTSRLTSFIERRK 3015  (SEQ ID NO:15)


 Score = 55.4 bits (131), Expect = 5e-06
 Identities = 42/153 (27%), Positives = 70/153 (45%), Gaps = 17/153 (11%)

Query: 1128 GRPEGLEKEGPPRKKPGLASFRLSGLKS----WDRAPTFLRELSDETVVLGQSVTLACQV 1183
            G+ EG  + G  + + GL++     L +    +D  P F+  LS+ T   G++V L C+V
Sbjct: 2590 GKREGKLENGYRKSREGLSNKVSVKLLNPNYIYDVPPEFVIPLSEVTCETGETVVLRCRV 2649

Query: 1184 SAQPAAQATW-SKDGAPLESSSRVLISATLKNFQLLTILVVVAEDLGVYTCSVSNALGTV 1242
              +P A  TW    +  L +     IS +      L I+ V  ED G+YTC    N +G+
Sbjct: 2650 CGRPKASITWKGPEHNTLNNDGHYSISYSDLGEATLKIVGVTTEDDGIYTCIAVNDMGSA 2709

Query: 1243 TTTGVLRKAERPSSSPCPDIGEVYADGVLLVWK 1275
            +++  LR             +     DG+++ WK
Sbjct: 2710 SSSASLR------------VLGPGMDGIMVTWK 2730  (SEQ ID NO:16)


 Score = 39.1 bits (89), Expect = 0.39
 Identities = 61/208 (29%), Positives = 76/208 (36%), Gaps = 65/208 (31%)

Query: 688  GGAPIRDMGHPQGSKQLPSTGGHPGTA--------QPERPSPD----------------S 723
            GGAP    GH  G    S GG P T+         QP R  P                 S
Sbjct: 2252 GGAPSGGSGHSGGPS---SCGGAPSTSRSRPSRIPQPVRHHPPVLVSSAASSQAEADKMS 2308
```

FIGURE 2H

```
Query: 724  PWGQPAPFCHPKQGSAPQEGCSPHPAVAPCPPGSFPPGSCKEAPLVPSSPFLGQPQ---- 779
            P P   P  G+AP+ G S   A +  PPG+   GS +EA  +P    L  P+
Sbjct: 2309 GTSTPGPSL-PPPGAAPEAGPS---APSRRPPGADAEGSEREAEPIPKMKVLESPRKGAA 2364

Query: 780  -----APPAPAK-----------------ASPPLDSKMGPGDISLPGRPKPGPCSSPGSA 817
                 +P APAK                   A+ PL+S +     SL   P P     P S
Sbjct: 2365 NASGSSPDAPAKDARASLGTLPLGKPRAGAASPLNSPLSSAVPSLGKEPFP-----PSSP 2419

Query: 818  SQASSSQVSSLRVG-SSQVG--TEPGPS 842
             Q   S  SS+    +S+ G  T PG S
Sbjct: 2420 LQKGGSFWSSIPASPASRPGSFTFPGDS 2447  (SEQ ID NO:17)

>gi|3024081|sp|Q15746|KMLS_HUMAN MYOSIN LIGHT CHAIN KINASE, SMOOTH
          MUSCLE AND NON-MUSCLE ISOZYMES (MLCK) [CONTAINS: TELOKIN]
          Length = 1913

 Score =  206 bits (518), Expect = 2e-51
 Identities = 104/298 (34%), Positives = 173/298 (57%), Gaps = 2/298 (0%)

Query: 159  RKLHSFYEVKEEIGRGVFGFVKRVQHKGNKILCAAKFIPLRSRTRAQAYRER-DILAALS 217
            +K+  FY+++E +G G FG V R+  K  + + A KF    S   +  R+   I+  L
Sbjct: 1458 QKVSDFYDIEERLGSGKFGQVFRLVEKKTRKVWAGKFFKAYSAKEKENIRQEISIMNCLH 1517

Query: 218  HPLVTGLLDQFETRKTLILILELCSSEELLDRLYRKGV-VTEAEVKVYIQQLVEGLHYLH 276
            HP +   +D FE +  ++++LE+ S  EL +R+  +   +TE E   Y++Q+ EG+ Y+H
Sbjct: 1518 HPKLVQCVDAFEEKANIVMVLEIVSGGELFERIIDEDFELTERECIKYMRQISEGVEYIH 1577

Query: 277  SHGVLHLDIKPSNILMVHPAREDIKICDFGFAQNITPAELQFSQYGSPEFVSPEIIQQNP 336
              G++HLD+KP NI+ V+      IK+ DFG A+ +  A       +G+PEFV+PE+I   P
Sbjct: 1578 KQGIVHLDLKPENIMCVNKTGTRIKLIDFGLARRLENAGSLKVLFGTPEFVAPEVINYEP 1637

Query: 337  VSEASDIWAMGVISYLSLTCSSPFAGESDRATLLNVLEGRVSWSSPMAAHLSEDAKDFIK 396
            +S A+D+W++GVI Y+ ++   SPF G++D  TL NV      +       +S+DAKDFI
Sbjct: 1638 ISYATDMWSIGVICYILVSGLSPFMGDNDNETLANVTSATWDFDDEAFDEISDDAKDFIS 1697

Query: 397  ATLQRAPQARPSAAQCLSHPWFLKSMPAEEAHFINTKQLKFLLARSRWQRSLMSYKSI 454
              L++  + R    QCL HPW +K     EA  ++  ++K  +AR +WQ++  + ++I
Sbjct: 1698 NLLKKDMKNRLDCTQCLQHPWLMKDTKNMEAKKLSKDRMKKYMARRKWQKTGNAVRAI 1755
 (SEQ ID NO:18)

 Score =  127 bits (315), Expect = 1e-27
 Identities = 134/528 (25%), Positives = 219/528 (41%), Gaps = 55/528 (10%)

Query: 1132 GLEKEGPPRKKPGLASFRLSGLKSWDRAPTFLRELSDETVVLGQSVTLACQVSAQPAAQA 1191
            G E +   +KKP   +   + +      P  ++   D+ V  G+SV L  +V+
Sbjct: 1215 GTESDATVKKKPAPKTPPKAAMP-----PQIIQFPEDQKVRAGESVELFGKVTGTQPITC 1269

Query: 1192 TWSKDGAPLESSSRVLISATLKNFQLLTILVVVAEDLGVYTCSVSNALGT----VTTTGV 1247
            TW K    ++ S  + +  + +N   LTIL    E  G YT  V N LG+    V  T V
Sbjct: 1270 TWMKFRKQIQDSEHIKVENS-ENGSKLTILAARQEHCGCYTLLVENKLGSRQAQVNLT-V 1327

Query: 1248 LRKAERPSSSPCPDIGEVYADGVLLVWKPVESYGPVTYIVQCSLE-----GGSWTTLASD 1302
            + K + P+ +PC    ++ +  + L W    SY   + +   S+E       +W  LA+
Sbjct: 1328 VDKPDPPAGTPCAS--DIRSSSLTLSWYG-SSYDGGSAVQSYSIEIWDSANKTWKELAT- 1383

Query: 1303 IFDCCYLTS----KLSRGGTYTFRTACVSKAGMGPYSSPSEQVLLGGPSHLAS------- 1351
                C  TS     L     Y FR   ++  G    S  SE   +G
Sbjct: 1384 ----CRSTSFNVQDLLPDHEYKFRVRAINVYGTSEPSQESELTTVGEKPEEPKMKWRCQT 1439

Query: 1352 ----EEESQGRSAQPLPSTKTFAF---QTQIQRGRFSVVRQCWEKASGRALAAKIIP-YH 1403
                E E.  R+       K   F   + ++  G+F  V +  EK + +  A K    Y
Sbjct: 1440 DDEKEPEVDYRTVTINTEQKVSDFYDIEERLGSGKFGQVFRLVEKKTRKVWAGKFFKAYS 1499

Query: 1404 PKDKTAVLREYEALKGLRHPHLAQLHAAYLSPRHLVLILELCSGPELLP-CLAERASYSE 1462
            K+K  + +E   + L HP L Q   A+    ++V++LE+ SG EL    + E    +E
Sbjct: 1500 AKEKENIRQEISIMNCLHHPKLVQCVDAFEEKANIVMVLEIVSGGELFERIIDEDFELTE 1559

Query: 1463 SEVKDYLWQMLSATQYLHNQHILHLDLRSENMIITEY--NLLKVVDLGNAQSLSQE---K 1517
            E   Y+ Q+    +Y+H Q I+HLDL+ EN++        +K++D G A+ L      K
Sbjct: 1560 RECIKYMRQISEGVEYIHKQGIVHLDLKPENIMCVNKTGTRIKLIDFGLARRLENAGSLK 1619

Query: 1518 VLPSDKFKDYLETMAPELLEGQGAVPQTDIWAIGVTAFIMLSAEYPVSSEGARDLQRGLR 1577
```

FIGURE 2I

```
           VL         E +APE++  +     TD+W+IGV  +I++S   P   +   +    +
Sbjct: 1620 VLFGTP-----EFVAPEVINYEPISYATDMWSIGVICYILVSGLSPFMGDNDNETLANVT 1674

Query: 1578 KGLVRL-SRCYAGLSGGAVAFLRSTLCAQPWGRPCASSCLQCPWLTEE 1624
                     +  +S   A   F+ + L       R   + CLQ PWL ++
Sbjct: 1675 SATWDFDDEAFDEISDDAKDFISNLLKKDMKNRLDCTQCLQHPWLMKD 1722  (SEQ ID NO:19)


 Score = 64.4 bits (154), Expect = 9e-09
 Identities = 36/106 (33%), Positives = 52/106 (48%), Gaps = 4/106 (3%)

Query: 54   PSMQVTIEDVQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLVDSTRLS-QQQEGTTYSLV 112
           P    TI D++   G   A+F+  IEG P P V W+KD    + +S         E    SL+
Sbjct: 1808 PYFSKTIRDLEVVEGSAARFDCKIEGYPDPEVVWFKDDQSIRESRHFQIDYDEDGNCSLI 1867

Query: 113  LRHVASKDAGVYTCLAQNTGGQVLCKAELLV---LGGDNEPDSEKQ 155
           +  V   D   YTC A N+ G+  C AEL+V     G+ E + E++
Sbjct: 1868 ISDVCGDDDAKYTCKAVNSLGEATCTAELIVETMEEGEGEGEEEEE 1913  (SEQ ID NO:20)


 Score = 64.0 bits (153), Expect = 1e-08
 Identities = 35/96 (36%), Positives = 46/96 (47%)

Query: 53   PPSMQVTIEDVQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLVDSTRLSQQQEGTTYSLV 112
           PP     +  V  + G    +F    I G PQP VTW K +V L  S R+S  ++      L
Sbjct: 160  PPKFATKLGRVVVKEGQMGRFSCKITGRPQPQVTWLKGNVPLQPSARVSVSEKNGMQVLE 219

Query: 113  LRHVASKDAGVYTCLAQNTGGQVLCKAELLVLGGDN 148
           +  V   D GVYTCL   N  G+    AEL + G D+
Sbjct: 220  IHGVNQDDVGVYTCLVVNGSGKASMSAELSIQGLDS 255  (SEQ ID NO:21)


 Score = 59.3 bits (141), Expect = 3e-07
 Identities = 30/100 (30%), Positives = 50/100 (50%), Gaps = 3/100 (3%)

Query: 47   LPALPGPPSMQVTIE---DVQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLVDSTRLSQQ 103
           LP  P  P+  + ++   D++   G         + G+P P V W  +  ++ +S     +
Sbjct: 613  LPVAPSKPTAPIFLQGLSDLKVMDGSQVTMTVQVSGNPPPEVIWLHNGNEIQESEDFHFE 672

Query: 104  QEGTTYSLVLRHVASKDAGVYTCLAQNTGGQVLCKAELLV 143
           Q GT +SL ++ V   +D G YTC A N+ G+V  +A L V
Sbjct: 673  QRGTQHSLWIQEVFPEDTGTYTCEAWNSAGEVRTQAVLTV 712  (SEQ ID NO:22)


 Score = 57.4 bits (136), Expect = 1e-06
 Identities = 32/89 (35%), Positives = 46/89 (50%), Gaps = 1/89 (1%)

Query: 1160 PTFLRELSDETVVLGQSVTLACQVSAQPAAQATWSKDGAPLESSSRVLISATLKNFQLLT 1219
           P F  +L    V  GQ    +C+++ +P  Q TW K   PL+ S+RV +S      Q+L
Sbjct: 161  PKFATKLGRVVVKEGQMGRFSCKITGRPQPQVTWLKGNVPLQPSARVSVSEK-NGMQVLE 219

Query: 1220 ILVVVAEDLGVYTCSVSNALGTVTTTGVL 1248
           I  V  +D+GVYTC V N  G  + +  L
Sbjct: 220  IHGVNQDDVGVYTCLVVNGSGKASMSAEL 248  (SEQ ID NO:23)


 Score = 53.5 bits (126), Expect = 2e-05
 Identities = 32/98 (32%), Positives = 46/98 (46%), Gaps = 4/98 (4%)

Query: 1159 APTFLRELSDETVVLGQSVTLACQVSAQPAAQATWSKDGAPLESSSRVLISATLKNFQLL 1218
           AP+F   L D  V+ GQ   L C V   P  + TW  +G P++ +     +   +   L
Sbjct: 513  APSFSSVLKDCAVIEGQDFVLQCSVRGTPVPRITWLLNGQPIQYARSTCEAGVAE----L 568

Query: 1219 TILVVVAEDLGVYTCSVSNALGTVTTTGVLRKAERPSS 1256
            I   + ED G YTC   NALG V+ +  +  E+ SS
Sbjct: 569  HIQDALPEDHGTYTCLAENALGQVSCSAWVTVHEKKSS 606  (SEQ ID NO:24)
```

FIGURE 2J

```
 Score = 53.1 bits (125), Expect = 2e-05
 Identities = 37/113 (32%), Positives = 48/113 (41%), Gaps = 1/113 (0%)

Query: 1140 RKKPGLASFRLSGLKSWDRAPTFLRELSDETVVLGQSVTLACQVSAQPAAQATWSKDGAP 1199
          +K    + + L    S   AP FL+ LSD  V+ G  VT+  QVS  P  +  W  +G
Sbjct: 603  KKSSRKSEYLLPVAPSKPTAPIFLQGLSDLKVMDGSQVTMTVQVSGNPPPEVIWLHNGNE 662

Query: 1200 LESSSRVLISATLKNFQLLTILVVVAEDLGVYTCSVSNALGTVTTTGVLRKAE 1252
          ++ S              L I  V  ED G YTC   N+ G V T  VL   E
Sbjct: 663  IQESEDFHFEQRGTQHS-LWIQEVFPEDTGTYTCEAWNSAGEVRTQAVLTVQE 714  (SEQ ID NO:25)


 Score = 51.9 bits (122), Expect = 5e-05
 Identities = 34/101 (33%), Positives = 50/101 (48%), Gaps = 2/101 (1%)

Query: 46   SLPALPGPPSMQVTIEDVQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLVDSTR-LSQQQ 104
          S+P L   P+  +   ++  + G TA+FE  + G P+P VTW+++   +    R L
Sbjct: 26   SMP-LTEAPAFILPPRNLCIKEGATAKFEGRVRGYPEPQVTWHRNGQPITSGGRFLLDCG 84

Query: 105  EGTTYSLVLRHVASKDAGVYTCLAQNTGGQVLCKAELLVLG 145
             T+SLV+  V  +D G YTC A N  G      EL V G
Sbjct: 85   IRGTFSLVIHAVHEEDRGKYTCEATNGSGARQVTVELTVEG 125  (SEQ ID NO:26)


 Score = 50.8 bits (119), Expect = 1e-04
 Identities = 41/182 (22%), Positives = 65/182 (35%), Gaps = 26/182 (14%)

Query: 1130 PEGLEKEGPPRKKPGLASFRLSGLKSWDRA----------PTFLRELSDETV 1171
          P G E++ P   +P     R  GL S D                P F  +   + V
Sbjct: 366  PSGEERKRPAPPRPATFPTRQPGLGSQDVVSKAANRRIPMEGQRDSAFPKFESKPQSQEV 425

Query: 1172 VLGQSVTLACQVSAQPAAQATWSKDGAPLESSSRVLISATLKNFQLLTILVVVAEDLGVY 1231
             Q+V   C+VS  P  +  W  +G P+      +          L +L     D G Y
Sbjct: 426  KENQTVKFRCEVSGIPKPEVAWFLEGTPVRRQEGSIEVYEDAGSHYLCLLKARTRDSGTY 485

Query: 1232 TCSVSNALGTVTTTGVLRKAERPSSSPCPDIGEVYADGVLLVWKPVESYGPVTYIVQCSL 1291
          +C+ SNA G V+ +  L+          P    V  D  ++  +         +++QCS+
Sbjct: 486  SCTASNAQGQVSCSWTLQVERLAVMEVAPSFSSVLKDCAVIEGQ--------DFVLQCSV 537

Query: 1292 EG 1293
           G
Sbjct: 538  RG 539  (SEQ ID NO:27)


 Score = 50.4 bits (118), Expect = 2e-04
 Identities = 26/100 (26%), Positives = 47/100 (47%), Gaps = 3/100 (3%)

Query: 54   PSMQVTIEDVQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLVDSTRLSQQQEGTTYSLVL 113
          P+ +  ++DV    G     +  +  DP  ++ W  +   L  +   QEG+  S+ +
Sbjct: 1098 PAFKQKLQDVHVAEGKKLLLQCQVSSDPPATIIWTLNGKTLKTTKFIILSQEGSLCSVSI 1157

Query: 114  RHVASKDAGVYTCLAQNTGGQVLCKAELLVLGGDNEPDSE 153
              +D G+Y C+A+N  GQ  C  ++ V   D+ P SE
Sbjct: 1158 EKALLEDRGLYKCVAKNDAGQAECSCQVTV---DDAPASE 1194  (SEQ ID NO:28)


 Score = 50.0 bits (117), Expect = 2e-04
 Identities = 35/125 (28%), Positives = 59/125 (47%), Gaps = 16/125 (12%)

Query: 1154 KSWDRAPTFLRELSDETVVLGQSVTLACQVSAQPAAQATWSKDGAPLESSSRVLISATLK 1213
          +S   AP F ++L D  V  G+ + L CQVS+ P A   W+ +G  L+++  +++S
Sbjct: 1092 ESQGTAPAFKQKLQDVHVAEGKKLLLQCQVSSDPPATIIWTLNGKTLKTTKFIILSQE-G 1150

Query: 1214 NFQLLTILVVVAEDLGVYTC----------SVSNALGTVTTTGVLRKAERPSSSP 1258
          +   ++I   + ED G+Y C                +V +A  +  T     K+ RP SS
Sbjct: 1151 SLCSVSIEKALLEDRGLYKCVAKNDAGQAECSCQVTVDDAPASENTKAPEMKSRRPKSSL 1210

Query: 1259 CPDIG 1263
           P +G
Sbjct: 1211 PPVLG 1215  (SEQ ID NO:29)
```

FIGURE 2K

```
 Score = 48.0 bits (112), Expect = 8e-04
 Identities = 26/87 (29%), Positives = 38/87 (42%)

Query: 1159 APTFLRELSDETVVLGQSVTLACQVSAQPAAQATWSKDGAPLESSSRVLISATLKNFQLL 1218
           AP F+    +  +  G +     +V   P  Q TW ++G P+ S  R L+   ++    L
Sbjct: 32   APAFILPPRNLCIKEGATAKFEGRVRGYPEPQVTWHRNGQPITSGGRFLLDCGIRGTFSL 91

Query: 1219 TILVVVAEDLGVYTCSVSNALGTVTTT 1245
            I  V  ED G YTC  +N  G    T
Sbjct: 92   VIHAVHEEDRGKYTCEATNGSGARQVT 118  (SEQ ID NO:30)


 Score = 45.3 bits (105), Expect = 0.005
 Identities = 37/140 (26%), Positives = 54/140 (38%), Gaps = 23/140 (16%)

Query: 22  TNHPSMVGCGWHPGLCGWGGGLHSSLPALPGPPSMQVTIEDVQAQTGGTAQFEAIIEGDP 81
           +N    V C W   +          L  +   PS    ++D     G     +  G P
Sbjct: 490 SNAQGQVSCSWTLQV--------ERLAVMEVAPSFSSVLKDCAVIEGQDFVLQCSVRGTP 541

Query: 82  QPSVTWYKDS--VQLVDSTRLSQQQEGTTYSLVLRHVASKDAGVYTCLAQNTGGQVLCKA 139
            P +TW  +   +Q   ST      E     L ++    +D G YTCLA+N  GQV C A
Sbjct: 542 VPRITWLLNGQPIQYARSTC-----EAGVAELHIQDALPEDHGTYTCLAENALGQVSCSA 596

Query: 140 ELLVLGGDNEPDSEKQSHRR 159
            + V         EK+S R+
Sbjct: 597 WVTV--------HEKKSSRK 608 (SEQ ID NO:31)


 Score = 44.5 bits (103), Expect = 0.009
 Identities = 26/104 (25%), Positives = 44/104 (42%), Gaps = 7/104 (6%)

Query: 41  GGLHSSLPALPGPPSMQVTIEDVQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLV-DSTR 99
           G   S+ P     P  Q      + +   T +F   + G P+P V W+ +   +
Sbjct: 407 GQRDSAFPKFESKPQSQ------EVKENQTVKFRCEVSGIPKPEVAWFLEGTPVRRQEGS 460

Query: 100 LSQQQEGTTYSLVLRHVASKDAGVYTCLAQNTGGQVLCKAELLV 143
           +   ++  ++ L L    ++D+G Y+C A N  GQV C   L V
Sbjct: 461 IEVYEDAGSHYLCLLKARTRDSGTYSCTASNAQGQVSCSWTLQV 504  (SEQ ID NO:32)


 Score = 44.1 bits (102), Expect = 0.012
 Identities = 26/82 (31%), Positives = 38/82 (45%), Gaps = 1/82 (1%)

Query: 63  VQAQTGGTAQFEAIIEGDPQPSVTWYKDSVQLV-DSTRLSQQQEGTTYSLVLRHVASKDA 121
           V A  G +      I GDP P+V W +D   L  D+      Q    ++LVL+ V    A
Sbjct: 730 VTASLGQSVLISCAIAGDPFPTVHWLRDGKALCKDTGHFEVLQNEDVFTLVLKKVQPWHA 789

Query: 122 GVYTCLAQNTGGQVLCKAELLV 143
           G Y  L +N  G+  C+  L++
Sbjct: 790 GQYEILLKNRVGECSCQVSLML 811  (SEQ ID NO:33)


 Score = 43.8 bits (101), Expect = 0.015
 Identities = 26/89 (29%), Positives = 35/89 (39%)

Query: 1160 PTFLRELSDETVVLGQSVTLACQVSAQPAAQATWSKDGAPLESSSRVLISATLKNFQLLT 1219
           P F + + D  VV G +    C++   P  +  W KD   +  S    I         L
Sbjct: 1808 PYFSKTIRDLEVVEGSAARFDCKIEGYPDPEVVWFKDDQSIRESRHFQIDYDEDGNCSLI 1867

Query: 1220 ILVVVAEDLGVYTCSVSNALGTVTTTGVL 1248
            I  V  +D   YTC   N+LG  T T  L
Sbjct: 1868 ISDVCGDDDAKYTCKAVNSLGEATCTAEL 1896 (SEQ ID NO:34)
```

FIGURE 2L

```
   1 CAGCACGAGG AACTCCTTCT GATCACCTGG CCAGCTGAGG TCAGAGTGGG
  51 AGAGGCAGTG GTTCCATTGA AGGAGTACTC CTAACTGTCA GAAGCCTGGG
 101 CGGTCAGGAT GGGGTGCTGT CGCTTGGGCT GCGGGGGGTG TTCAGTTGCC
 151 CACAGTGTAT CTCAGGGTCT CACCAACCAT CCAAGCATGG TAGGCTGTGG
 201 CTGGCACCCA GGGTTGTGTG GCTGGGGAGG TGGTCTCCAC AGTTCCCTCC
 251 CTGCCCTCCC AGGGCCCCCA TCCATGCAGG TAACCATCGA GGATGTGCAG
 301 GCACAGACAG GCGGAACGGC CCAATTCGAG GCTATCATTG AGGGCGACCC
 351 ACAGCCCTCG GTGACCTGGT ACAAGGACAG CGTCCAGCTG GTGGACAGCA
 401 CCCGGCTTAG CCAGCAGCAA GAAGGCACCA CATACTCCCT GGTGCTGAGG
 451 CATGTGGCCT CGAAGGATGC CGGCGTTTAC ACCTGCCTGG CCCAAAACAC
 501 TGGTGGCCAG GTGCTCTGCA AGGCAGAGCT GCTGGTGCTT GGGGGGGACA
 551 ATGAGCCGGA CTCAGAGAAG CAAAGCCACC GGAGGAAGCT GCACTCCTTC
 601 TATGAGGTCA AGGAGGAGAT TGGAAGGGGC GTGTTTGGCT TCGTAAAAAG
 651 AGTGCAGCAC AAAGGAAACA AGATCTTGTG CGCTGCCAAG TTCATCCCCC
 701 TACGGAGCAG AACTCGGGCC CAGGCATACA GGGAGCGAGA CATCCTGGCC
 751 GCGCTGAGCC ACCCGCTGGT CACGGGGCTG CTGGACCAGT TTGAGACCCG
 801 CAAGACCCTC ATCCTCATCC TGGAGCTGTG CTCATCCGAG GAGCTGCTGG
 851 ACCGCCTGTA CAGGAAGGGC GTGGTGACGG AGGCCGAGGT CAAGGTCTAC
 901 ATCCAGCAGC TGGTGGAGGG GCTGCACTAC CTGCACAGCC ATGGCGTTCT
 951 CCACCTGGAC ATAAAGCCCT CTAACATCCT GATGGTGCAT CCTGCCCGGG
1001 AAGACATTAA AATCTGCGAC TTTGGCTTTG CCCAGAACAT CACCCCAGCA
1051 GAGCTGCAGT TCAGCCAGTA CGGCTCCCCT GAGTTCGTCT CCCCCGAGAT
1101 CATCCAGCAG AACCCTGTGA GCGAAGCCTC CGACATTTGG GCCATGGGTG
1151 TCATCTCCTA CCTCAGCCTG ACCTGCTCAT CCCCATTTGC CGGCGAGAGT
1201 GACCGTGCCA CCCTCCTGAA CGTCCTGGAG GGGCGCGTGT CATGGAGCAG
1251 CCCCATGGCT GCCCACCTCA GCGAAGACGC CAAAGACTTC ATCAAGGCTA
1301 CGCTGCAGAG AGCCCCTCAG GCCCGGCCTA GTGCGGCCCA GTGCCTCTCC
1351 CACCCCTGGT TCCTGAAATC CATGCCTGCG GAGGAGGCCC ACTTCATCAA
1401 CACCAAGCAG CTCAAGTTCC TCCTGGCCCG AAGTCGCTGG CAGCGTTCCC
1451 TGATGAGCTA CAAGTCCATC CTGGTGATGC GCTCCATCCC TGAGCTGCTG
1501 CGGGGCCCAC CCGACAGCCC CTCCCTCGGC GTAGCCCGGC ACCTCTGCAG
1551 GGACACTGGT GGCTCCTCCA GTTCCTCCTC CTCCTCTGAC AACGAGCTCG
1601 CCCCATTTGC CCGGGCTAAG TCACTGCCAC CCTCCCCGGT GACACACTCA
1651 CCACTGCTGC ACCCCCGGGG CTTCCTGCGG CCCTCGGCCA GCCTGCCTGA
1701 GGAAGCCGAG GCCAGTGAGC GCTCCACCGA GGCCCCAGCT CCGCCTGCAT
1751 CTCCCGAGGG TGCCGGGCCA CCGGCCGCCC AGGGCTGCGT GCCCCGGCAC
1801 AGCGTCATCC GCAGCCTGTT CTACCACCAG GCGGGTGAGA GCCCTGAGCA
1851 CGGGGCCCTG GCCCCGGGGA GCAGGCGGCA CCCGGCCCGG CGGCGGCACC
1901 TGCTGAAGGG CGGCTACATT GCGGGGGCGC TGCCAGGCCT GCGCGAGCCA
1951 CTGATGGAGC ACCGCGTGCT GGAGGAGGAG GCCGCCAGGG AGGAGCAGGC
2001 CACCCTCCTG GCCAAAGCCC CCTCATTCGA GACTGCCCTC CGGCTGCCTG
2051 CCTCTGGCAC CCACTTGGCC CCTGGCCACA GCCACTCCCT GGAACATGAC
2101 TCTCCGAGCA CCCCCCGCCC CTCCTCGGAG GCCTGCGGTG AGGCACAGCG
2151 ACTGCCTTCA GCCCCCTCCG GGGGGGCCCC TATCAGGGAC ATGGGGCACC
2201 CTCAGGGCTC CAAGCAGCTT CCATCCACTG GTGGCCACCC AGGCACTGCT
2251 CAGCCAGAGA GGCCATCCCC GGACAGCCCT TGGGGGCAGC CAGCCCCTTT
2301 CTGCCACCCC AAGCAGGGTT CTGCCCCCCA GGAGGGCTGC AGCCCCCACC
2351 CAGCAGTTGC CCCATGCCCT CCTGGCTCCT TCCCTCCAGG ATCTTGCAAA
2401 GAGGCCCCCT TAGTACCCTC AAGCCCCTTC TTGGGACAGC CCCAGGCACC
2451 CCCTGCCCCT GCCAAAGCAA GCCCCCCATT GGACTCTAAG ATGGGGCCTG
2501 GAGACATCTC TCTTCCTGGG AGGCCAAAAC CCGGCCCCTG CAGTTCCCCA
2551 GGGTCAGCCT CCCAGGCGAG CTCTTCCCAA GTGAGCTCCC TCAGGGTGGG
2601 CTCCTCCCAG GTGGGCACAG AGCCTGGCCC CTCCCTGGAT GCGGAGGGCT
2651 GGACCCAGGA GGCTGAGGAT CTGTCCGACT CCACACCCAC CTTGCAGCGG
2701 CCTCAGGAAC AGGTGACCAT GCGCAAGTTC TCCCTGGGTG GTCGCGGGGG
2751 CTACGCAGGC GTGGCTGGCT ATGGCACCTT TGCCTTTGGT GGAGATGCAG
2801 GGGGCATGCT GGGGCAGGGG CCCATGTGGG CCAGGATAGC CTGGGCTGTG
2851 TCCCAGTCGG AGGAGGAGGA GCAGGAGGAG GCCAGGGCTG AGTCCCAGTC
2901 GGAGGAGCAG CAGGAGGCCA GGGCTGAGAG CCCACTGCCC CAGGTCAGTG
2951 CAAGGCCTGT GCCTGAGGTC GGCAGGGCTC CCACCAGGAG CTCTCCAGAG
3001 CCCACCCCAT GGGAGGACAT CGGGCAGGTC TCCCTGGTGC AGATCCGGGA
3051 CCTGTCAGGT GATGCGGAGG CGGCCGACAC AATATCCCTG GACATTTCCG
3101 AGGTGGACCC CGCCTACCTC AACCTCTCAG ACCTGTACGA TATCAAGTAC
3151 CTCCCATTCG AGTTTATGAT CTTCAGGAAA GTCCCCAAGT CCGCTCAGCC
3201 AGAGCCGCCC TCCCCCATGG CTGAGGAGGA GCTGGCCGAG TTCCCGGAGC
3251 CCACGTGGCC CTGGCCAGGT GAACTGGGCC CCCACGCAGG CCTGGAGATC
3301 ACAGAGGAGT CAGAGGATGT GGACGCGCTG CTGGCAGAGG CTGCCGTGGG
3351 CAGGAAGCGC AAGTGGTCCT CGCCGTCACG CAGCCTCTTC CACTTCCCTG
3401 GGAGGCACCT GCCGCTGGAT GAGCCTGCAG AGCTGGGGCT GCGTGAGAGA
3451 GTGAAGGCCT CCGTGGAGCA CATCTCCCGG ATCCTGAAGG GCAGGCCGGA
3501 AGGTCTGGAG AAGGAGGGGC CCCCCAGGAA GAAGCCAGGC CTTGCTTCCT
3551 TCCGGCTCTC AGGTCTGAAG AGCTGGGACC GAGCGCCGAC ATTCCTAAGG
3601 GAGCTCTCAG ATGAGACTGT GGTCCTGGGC CAGTCAGTGA CACTGGCCTG
```

FIGURE 3A

```
3651 CCAGGTGTCA GCCCAGCCAG CTGCCCAGGC CACCTGGAGC AAAGACGGAG
3701 CCCCCCTGGA GAGCAGCAGC CGTGTCCTCA TCTCTGCCAC CCTCAAGAAC
3751 TTCCAGCTTC TGACCATCCT GGTGGTGGTG GCTGAGGACC TGGGTGTGTA
3801 CACCTGCAGC GTGAGCAATG CGCTGGGGAC AGTGACCACC ACGGGCGTCC
3851 TCCGGAAGGC AGAGCGCCCC TCATCTTCGC CATGCCCGGA TATCGGGGAG
3901 GTGTACGCGG ATGGGGTGCT GCTGGTCTGG AAGCCCGTGG AATCCTACGG
3951 CCCTGTGACC TACATTGTGC AGTGCAGCCT AGAAGGCGGC AGCTGGACCA
4001 CACTGGCCTC CGACATCTTT GACTGCTGCT ACCTGACCAG CAAGCTCTCC
4051 CGGGGTGGCA CCTACACCTT CCGCACGGCA TGTGTCAGCA AGGCAGGAAT
4101 GGGTCCCTAC AGCAGCCCCT CGGAGCAAGT CCTCCTGGGA GGGCCCAGCC
4151 ACCTGGCCTC TGAGGAGGAG AGCCAGGGGC GGTCAGCCCA ACCCCTGCCC
4201 AGCACAAAGA CCTTCGCATT CCAGACACAG ATCCAGAGGG GCCGCTTCAG
4251 CGTGGTGCGG CAATGCTGGG AGAAGGCCAG CGGGCGGGCG CTGGCCGCCA
4301 AGATCATCCC CTACCACCCC AAGGACAAGA CAGCAGTGCT GCGCGAATAC
4351 GAGGCCCTCA AGGGCCTGCG CCACCCGCAC CTGGCCCAGC TGCACGCAGC
4401 CTACCTCAGC CCCCGGCACC TGGTGCTCAT CTTGGAGCTG TGCTCTGGGC
4451 CCGAGCTGCT CCCCTGCCTG GCCGAGAGGG CCTCCTACTC AGAATCTGAG
4501 GTGAAGGACT ACCTGTGGCA GATGTTGAGT GCCACCCAGT ACCTGCACAA
4551 CCAGCACATC CTGCACCTGG ACCTGAGGTC CGAGAACATG ATCATCACCG
4601 AATACAACCT GCTCAAGGTC GTGGACCTGG GCAATGCACA GAGCCTCAGC
4651 CAGGAGAAGG TGCTGCCCTC AGACAAGTTC AAGGACTACC TAGAGACCAT
4701 GGCTCCAGAG CTCCTGGAGG GCCAGGGGGC TGTTCCACAG ACAGACATCT
4751 GGGCCATCGG TGTGACAGCC TTCATCATGC TGAGCGCCGA GTACCCGGTG
4801 AGCAGCGAGG GTGCACGCGA CCTGCAGAGA GGACTGCGCA AGGGGCTGGT
4851 CCGGCTGAGC CGCTGCTACG CGGGGCTGTC CGGGGGCGCC GTGGCCTTCC
4901 TGCGCAGCAC TCTGTGCGCC CAGCCCTGGG GCCGGCCCTG CGCGTCCAGC
4951 TGCCTGCAGT GCCCGTGGCT AACAGAGGAG GGCCCGGCCT GTTCGCGGCC
5001 CGCGCCCGTG ACCTTCCCTA CCGCGCGGCT GCGCGTCTTC GTGCGCAATC
5051 GCGAGAAGAG ACGCGCGCTG CTGTACAAGA GGCACAACCT GGCCCAGGTG
5101 CGCTGAGGGT CGCCCCGGCC ACACCCTTGG TCTCCCCGCT GGGGGTCGCT
5151 GCAGACGCGC CAATAAAAAC GCACAGCCGG GCGAGAAAAA AAAAAAAAAA
5201 AAAAAAA  (SEQ ID NO:3)
```

FEATURES:

Start: 109
Exon: 109-5103
Stop: 5104

SNPs:

DNA Position	Major	Minor	Domain	Protein Position	Major	Minor
311	T	C G	Exon	68	V	A G
1741	C	T	Exon	545	P	S
2714	T	C	Exon	869	V	A
2745	C	T	Exon	879	R	R
2859	A	G	Exon	917	S	S
3420	T	C	Exon	1104	D	D

Context:

DNA Position

```
311     AACTCCTTCTGATCACCTGGCCAGCTGAGGTCAGAGTGGGAGAGGCAGTGGTTCCATTGA
        AGGAGTACTCCTAACTGTCAGAAGCCTGGGCGGTCAGGATGGGGTGCTGTCGCTTGGGCT
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        TAGGCTGTGGCTGGCACCCAGGGTTGTGTGGCTGGGGAGGTGGTCTCCACAGTTCCCTCC
        CTGCCCTCCCAGGGCCCCCATCCATGCAGGTAACCATCGAGGATGTGCAGGCACAGACAG
        [T,C,G]
        CGGAACGGCCCAATTCGAGGCTATCATTGAGGGCGACCCACAGCCCTCGGTGACCTGGTA
        CAAGGACAGCGTCCAGCTGGTGGACAGCACCCGGCTTAGCCAGCAGCAAGAAGGCACCAC
        ATACTCCCTGGTGCTGAGGCATGTGGCCTCGAAGGATGCCGGCGTTTACACCTGCCTGGC
        CCAAAACACTGGTGGCCAGGTGCTCTGCAAGGCAGAGCTGCTGGTGCTTGGGGGGGACAA
        TGAGCCGGACTCAGAGAAGCAAAGCCACCGGAGGAAGCTGCACTCCTTCTATGAGGTCAA
```

FIGURE 3B

```
1741    CAGCGTTCCCTGATGAGCTACAAGTCCATCCTGGTGATGCGCTCCATCCCTGAGCTGCTG
        CGGGGCCCACCCGACAGCCCCTCCCTCGGCGTAGCCCGGCACCTCTGCAGGGACACTGGT
        GGCTCCTCCAGTTCCTCCTCCTCCTCTGACAACGAGCTCGCCCCATTTGCCCGGGCTAAG
        TCACTGCCACCCTCCCCGGTGACACACTCACCACTGCTGCACCCCCGGGGCTTCCTGCGG
        CCCTCGGCCAGCCTGCCTGAGGAAGCCGAGGCCAGTGAGCGCTCCACCGAGGCCCCAGCT
        [C,T]
        CGCCTGCATCTCCCGAGGGTGCCGGGCCACCGGCCGCCCAGGGCTGCGTGCCCCGGCACA
        GCGTCATCCGCAGCCTGTTCTACCACCAGGCGGGTGAGAGCCCTGAGCACGGGGCCCTGG
        CCCCGGGGAGCAGGCGGCACCCGGCCCGGCGGCGGCACCTGCTGAAGGGCGGCTACATTG
        CGGGGGCGCTGCCAGGCCTGCGCGAGCCACTGATGGAGCACCGCGTGCTGGAGGAGGAGG
        CCGCCAGGGAGGAGCAGGCCACCCTCCTGGCCAAAGCCCCCTCATTCGAGACTGCCCTCC

2714    TACCCTCAAGCCCCTTCTTGGGACAGCCCCAGGCACCCCCTGCCCCTGCCAAAGCAAGCC
        CCCCATTGGACTCTAAGATGGGGCCTGGAGACATCTCTCTTCCTGGGAGGCCAAAACCCG
        GCCCCTGCAGTTCCCCAGGGTCAGCCTCCCAGGCGAGCTCTTCCCAAGTGAGCTCCCTCA
        GGGTGGGCTCCTCCCAGGTGGGCACAGAGCCTGGCCCCTCCCTGGATGCGGAGGGCTGGA
        CCCAGGAGGCTGAGGATCTGTCCGACTCCACACCCACCTTGCAGCGGCCTCAGGAACAGG
        [T,C]
        GACCATGCGCAAGTTCTCCCTGGGTGGTCGCGGGGGCTACGCAGGCGTGGCTGGCTATGG
        CACCTTTGCCTTTGGTGGAGATGCAGGGGGCATGCTGGGGCAGGGGCCCATGTGGGCCAG
        GATAGCCTGGGCTGTGTCCCAGTCGGAGGAGGAGGAGCAGGAGGAGGCCAGGGCTGAGTC
        CCAGTCGGAGGAGCAGCAGGAGGCCAGGGCTGAGAGCCCACTGCCCCAGGTCAGTGCAAG
        GCCTGTGCCTGAGGTCGGCAGGGCTCCCACCAGGAGCTCTCCAGAGCCCACCCCATGGGA

2745    GGCACCCCCTGCCCCTGCCAAAGCAAGCCCCCCATTGGACTCTAAGATGGGGCCTGGAGA
        CATCTCTCTTCCTGGGAGGCCAAAACCCGGCCCCCTGCAGTTCCCCAGGGTCAGCCTCCCA
        GGCGAGCTCTTCCCAAGTGAGCTCCCTCAGGGTGGGCTCCTCCCAGGTGGGCACAGAGCC
        TGGCCCCTCCCTGGATGCGGAGGGCTGGACCCAGGAGGCTGAGGATCTGTCCGACTCCAC
        ACCCACCTTGCAGCGGCCTCAGGAACAGGTGACCATGCGCAAGTTCTCCCTGGGTGGTCG
        [C,T]
        GGGGGCTACGCAGGCGTGGCTGGCTATGGCACCTTTGCCTTTGGTGGAGATGCAGGGGGC
        ATGCTGGGGCAGGGGCCCATGTGGGCCAGGATAGCCTGGGCTGTGTCCCAGTCGGAGGAG
        GAGGAGCAGGAGGAGGCCAGGGCTGAGTCCCAGTCGGAGGAGCAGCAGGAGGCCAGGGCT
        GAGAGCCCACTGCCCCAGGTCAGTGCAAGGCCTGTGCCTGAGGTCGGCAGGGCTCCCACC
        AGGAGCTCTCCAGAGCCCACCCCATGGGAGGACATCGGGCAGGTCTCCCTGGTGCAGATC

2859    CTCCCAGGCGAGCTCTTCCCAAGTGAGCTCCCTCAGGGTGGGCTCCTCCCAGGTGGGCAC
        AGAGCCTGGCCCCTCCCTGGATGCGGAGGGCTGGACCCAGGAGGCTGAGGATCTGTCCGA
        CTCCACACCCACCTTGCAGCGGCCTCAGGAACAGGTGACCATGCGCAAGTTCTCCCTGGG
        TGGTCGCGGGGGCTACGCAGGCGTGGCTGGCTATGGCACCTTTGCCTTTGGTGGAGATGC
        AGGGGGCATGCTGGGGCAGGGGCCCATGTGGGCCAGGATAGCCTGGGCTGTGTCCCAGTC
        [A,G]
        GAGGAGGAGGAGCAGGAGGAGGCCAGGGCTGAGTCCCAGTCGGAGGAGCAGCAGGAGGCC
        AGGGCTGAGAGCCCACTGCCCCAGGTCAGTGCAAGGCCTGTGCCTGAGGTCGGCAGGGCT
        CCCACCAGGAGCTCTCCAGAGCCCACCCCATGGGAGGACATCGGGCAGGTCTCCCTGGTG
        CAGATCCGGGACCTGTCAGGTGATGCGGAGGCGGCCGACACAATATCCCTGGACATTTCC
        GAGGTGGACCCCGCCTACCTCAACCTCTCAGACCTGTACGATATCAAGTACCTCCCATTC

3420    CAACCTCTCAGACCTGTACGATATCAAGTACCTCCCATTCGAGTTTATGATCTTCAGGAA
        AGTCCCCAAGTCCGCTCAGCCAGAGCCGCCCTCCCCCATGGCTGAGGAGGAGCTGGCCGA
        GTTCCCGGAGCCCACGTGGCCCTGGCCAGGTGAACTGGGCCCCCACGCAGGCCTGGAGAT
        CACAGAGGAGTCAGAGGATGTGGACGCGCTGCTGGCAGAGGCTGCCGTGGGCAGGAAGCG
        CAAGTGGTCCTCGCCGTCACGCAGCCTCTTCCACTTCCCTGGGAGGCACCTGCCGCTGGA
        [T,C]
        GAGCCTGCAGAGCTGGGGCTGCGTGAGAGAGTGAAGGCCTCCGTGGAGCACATCTCCCGG
        ATCCTGAAGGGCAGGCCGGAAGGTCTGGAGAAGGAGGGGCCCCCCAGGAAGAAGCCAGGC
        CTTGCTTCCTTCCGGCTCTCAGGTCTGAAGAGCTGGGACCGAGCGCCGACATTCCTAAGG
        GAGCTCTCAGATGAGACTGTGGTCCTGGGCCAGTCAGTGACACTGGCCTGCCAGGTGTCA
        GCCCAGCCAGCTGCCCAGGCCACCTGGAGCAAAGACGGAGCCCCCCTGGAGAGCAGCAGC
```

Chromosome map position: 1

Bac accession number: AC023889

FIGURE 3C

SEQUENCE LISTING

<110> PE CORPORATION (NY)

<120> ISOLATED HUMAN KINASE PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN KINASE PROTEINS, AND USES THEREOF

<130> CL000927PCT

<140> TO BE ASSIGNED
<141> 2001-22-10

<150> 09/858,664
<151> 2001-17-05

<150> 09/711,134
<151> 2000-14-11

<160> 34

<170> FastSEQ for Windows Version 4.0

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<211> 5207
<212> DNA
<213> Human

<400> 1
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gttccattga aggagtactc ctaactgtca gaagcctggg cggtcaggat ggggtgctgt 120
cgcttgggct gcgggggggtg ttcagttgcc cacagtgtat ctcagggtct caccaaccat 180
ccaagcatgg taggctgtgg ctggcaccca gggttgtgtg gctggggagg tggtctccac 240
agttccctcc ctgccctccc agggccccca tccatgcagg taaccatcga ggatgtgcag 300
gcacagacag gcggaacggc ccaattcgag gctatcattg agggcgaccc acagccctcg 360
gtgacctggt acaaggacag cgtccagctg gtggacagca cccggcttag ccagcagcaa 420
gaaggcacca catactccct ggtgctgagg catgtggcct cgaaggatgc cggcgtttac 480
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ctggaccagt ttgagacccg caagaccctc atcctcatcc tggagctgtg ctcatccgag 840
gagctgctgg accgcctgta caggaagggc gtggtgacgg aggccgaggt caaggtctac 900
atccagcagc tggtggaggg gctgcactac ctgcacagcc atggcgttct ccacctggac 960
ataaagccct ctaacatcct gatggtgcat cctgcccggg aagacattaa aatctgcgac 1020
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        35                  40                  45
Ala Leu Pro Gly Pro Pro Ser Met Gln Val Thr Ile Glu Asp Val Gln
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Ala Gln Thr Gly Gly Thr Ala Gln Phe Glu Ala Ile Ile Glu Gly Asp
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Pro Gln Pro Ser Val Thr Trp Tyr Lys Asp Ser Val Gln Leu Val Asp
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Ser Thr Arg Leu Ser Gln Gln Gln Glu Gly Thr Thr Tyr Ser Leu Val
            100                 105                 110
Leu Arg His Val Ala Ser Lys Asp Ala Gly Val Tyr Thr Cys Leu Ala
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Gln Asn Thr Gly Gly Gln Val Leu Cys Lys Ala Glu Leu Leu Val Leu
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Gly Gly Asp Asn Glu Pro Asp Ser Glu Lys Gln Ser His Arg Arg Lys
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Gly Phe Val Lys Arg Val Gln His Lys Gly Asn Lys Ile Leu Cys Ala
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Ala Lys Phe Ile Pro Leu Arg Ser Arg Thr Arg Ala Gln Ala Tyr Arg
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Glu Arg Asp Ile Leu Ala Ala Leu Ser His Pro Leu Val Thr Gly Leu
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Cys Ser Ser Glu Glu Leu Leu Asp Arg Leu Tyr Arg Lys Gly Val Val
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Thr Glu Ala Glu Val Lys Val Tyr Ile Gln Gln Leu Val Glu Gly Leu
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His Tyr Leu His Ser His Gly Val Leu His Leu Asp Ile Lys Pro Ser
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Asn Ile Leu Met Val His Pro Ala Arg Glu Asp Ile Lys Ile Cys Asp
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Phe Gly Phe Ala Gln Asn Ile Thr Pro Ala Glu Leu Gln Phe Ser Gln
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Tyr Gly Ser Pro Glu Phe Val Ser Pro Glu Ile Ile Gln Gln Asn Pro
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Val Ser Glu Ala Ser Asp Ile Trp Ala Met Gly Val Ile Ser Tyr Leu
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Trp Phe Leu Lys Ser Met Pro Ala Glu Glu Ala His Phe Ile Asn Thr
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Lys Gln Leu Lys Phe Leu Leu Ala Arg Ser Arg Trp Gln Arg Ser Leu
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His Ser Pro Leu Leu His Pro Arg Gly Phe Leu Arg Pro Ser Ala Ser
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His Ser His Ser Leu Glu His Asp Ser Pro Ser Thr Pro Arg Pro Ser
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Pro Asp Ser Pro Trp Gly Gln Pro Ala Pro Phe Cys His Pro Lys Gln
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Gly Ser Ala Pro Gln Glu Gly Cys Ser Pro His Pro Ala Val Ala Pro
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Cys Pro Pro Gly Ser Phe Pro Pro Gly Ser Cys Lys Glu Ala Pro Leu
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Val Pro Ser Ser Pro Phe Leu Gly Gln Pro Gln Ala Pro Pro Ala Pro
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Ala Lys Ala Ser Pro Pro Leu Asp Ser Lys Met Gly Pro Gly Asp Ile
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Ser Gln Val Gly Thr Glu Pro Gly Pro Ser Leu Asp Ala Glu Gly Trp
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Thr Gln Glu Ala Glu Asp Leu Ser Asp Ser Thr Pro Thr Leu Gln Arg
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Pro Gln Glu Gln Val Thr Met Arg Lys Phe Ser Leu Gly Gly Arg Gly
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Gly Tyr Ala Gly Val Ala Gly Tyr Gly Thr Phe Ala Phe Gly Gly Asp
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Ala Gly Gly Met Leu Gly Gln Gly Pro Met Trp Ala Arg Ile Ala Trp
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Val Gln Ile Arg Asp Leu Ser Gly Asp Ala Glu Ala Ala Asp Thr Ile
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Ser Leu Asp Ile Ser Glu Val Asp Pro Ala Tyr Leu Asn Leu Ser Asp
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Leu Tyr Asp Ile Lys Tyr Leu Pro Phe Glu Phe Met Ile Phe Arg Lys
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Glu Gly Gln Gly Ala Val Pro Gln Thr Asp Ile Trp Ala Ile Gly Val
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gtgtacgcgg atggggtgct gctggtctgg aagcccgtgg aatcctacgg ccctgtgacc 3960
tacattgtgc agtgcagcct agaaggcggc agctggacca cactggcctc cgacatcttt 4020
gactgctgct acctgaccag caagctctcc cggggtggca cctacacctt ccgcacggca 4080
tgtgtcagca aggcaggaat gggtccctac agcagcccct cggagcaagt cctcctggga 4140
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agcacaaaga ccttcgcatt ccagacacag atccagaggg gccgcttcag cgtggtgcgg 4260
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aaggacaaga cagcagtgct gcgcgaatac gaggccctca agggcctgcg ccacccgcac 4380
ctggcccagc tgcacgcagc ctacctcagc ccccggcacc tggtgctcat cttggagctg 4440
tgctctgggc ccgagctgct cccctgcctg gccgagaggg cctcctactc agaatctgag 4500
gtgaaggact acctgtggca gatgttgagt gccacccagt acctgcacaa ccagcacatc 4560
ctgcacctgg acctgaggtc cgagaacatg atcatcaccg aatacaacct gctcaaggtc 4620
gtggacctgg gcaatgcaca gagcctcagc caggagaagg tgctgccctc agacaagttc 4680
aaggactacc tagagaccat ggctccagag ctcctggagg gccagggggc tgttccacag 4740
acagacatct gggccatcgg tgtgacagcc ttcatcatgc tgagcgccga gtacccggtg 4800
agcagcgagg gtgcacgcga cctgcagaga ggactgcgca aggggctggt ccggctgagc 4860
cgctgctacg cggggctgtc cgggggcgcc gtggccttcc tgcgcagcac tctgtgcgcc 4920

```
cagccctggg gccggccctg cgcgtccagc tgcctgcagt gcccgtggct aacagaggag 4980
ggcccggcct gttcgcggcc cgcgcccgtg accttcccta ccgcgcggct gcgcgtcttc 5040
gtgcgcaatc gcgagaagag acgcgcgctg ctgtacaaga ggcacaacct ggcccaggtg 5100
cgctgagggt cgccccggcc acacccttgg tctccccgct gggggtcgct gcagacgcgc 5160
caataaaaac gcacagccgg gcgagaaaaa aaaaaaaaaa aaaaaaa                5207
```

<210> 4
<211> 846
<212> PRT
<213> Human

<400> 4

```
Pro Arg Phe Glu Ser Ile Met Glu Asp Val Glu Val Gly Ala Gly Glu
 1               5                  10                  15
Thr Ala Arg Phe Ala Val Val Val Glu Gly Lys Pro Leu Pro Asp Ile
            20                  25                  30
Met Trp Tyr Lys Asp Glu Val Leu Leu Thr Glu Ser Ser His Val Ser
        35                  40                  45
Phe Val Tyr Glu Glu Asn Glu Cys Ser Leu Val Val Leu Ser Thr Gly
    50                  55                  60
Ala Gln Asp Gly Gly Val Tyr Thr Cys Thr Ala Gln Asn Leu Ala Gly
65                  70                  75                  80
Glu Val Ser Cys Lys Ala Glu Leu Ala Val His Ser Ala Gln Thr Ala
                85                  90                  95
Met Glu Val Glu Gly Val Gly Glu Asp Glu Asp His Arg Gly Arg Arg
            100                 105                 110
Leu Ser Asp Phe Tyr Asp Ile His Gln Glu Ile Gly Arg Gly Ala Phe
        115                 120                 125
Ser Tyr Leu Arg Arg Ile Val Glu Arg Ser Ser Gly Leu Glu Phe Ala
    130                 135                 140
Ala Lys Phe Ile Pro Ser Gln Ala Lys Pro Lys Ala Ser Ala Arg Arg
145                 150                 155                 160
Glu Ala Arg Leu Leu Ala Arg Leu Gln His Asp Cys Val Leu Tyr Phe
                165                 170                 175
His Glu Ala Phe Glu Arg Arg Arg Gly Leu Val Ile Val Thr Glu Leu
            180                 185                 190
Cys Thr Glu Glu Leu Leu Glu Arg Ile Ala Arg Lys Pro Thr Val Cys
        195                 200                 205
Glu Ser Glu Ile Arg Ala Tyr Met Arg Gln Val Leu Glu Gly Ile His
    210                 215                 220
Tyr Leu His Gln Ser His Val Leu His Leu Asp Val Lys Pro Glu Asn
225                 230                 235                 240
Leu Leu Val Trp Asp Gly Ala Ala Gly Glu Gln Gln Val Arg Ile Cys
                245                 250                 255
Asp Phe Gly Asn Ala Gln Glu Leu Thr Pro Gly Glu Pro Gln Tyr Cys
            260                 265                 270
Gln Tyr Gly Thr Pro Glu Phe Val Ala Pro Glu Ile Val Asn Gln Ser
        275                 280                 285
Pro Val Ser Gly Val Thr Asp Ile Trp Pro Val Gly Val Val Ala Phe
    290                 295                 300
Leu Cys Leu Thr Gly Ile Ser Pro Phe Val Gly Glu Asn Asp Arg Thr
305                 310                 315                 320
Thr Leu Met Asn Ile Arg Asn Tyr Asn Val Ala Phe Glu Glu Thr Thr
                325                 330                 335
Phe Leu Ser Leu Ser Arg Glu Ala Arg Gly Phe Leu Ile Lys Val Leu
            340                 345                 350
Val Gln Asp Arg Leu Arg Pro Thr Ala Glu Glu Thr Leu Glu His Pro
        355                 360                 365
Trp Phe Lys Thr Gln Ala Lys Gly Ala Glu Val Ser Thr Asp His Leu
```

```
    370                 375                 380
Lys Leu Phe Leu Ser Arg Arg Arg Trp Gln Arg Ser Gln Ile Ser Tyr
385                 390                 395                 400
Lys Cys His Leu Val Leu Arg Pro Ile Pro Glu Leu Leu Arg Ala Pro
                405                 410                 415
Pro Glu Arg Val Trp Val Thr Met Pro Arg Arg Pro Pro Pro Ser Gly
            420                 425                 430
Gly Leu Ser Ser Ser Ser Asp Ser Glu Glu Glu Glu Leu Glu Glu Leu
        435                 440                 445
Pro Ser Val Pro Arg Pro Leu Gln Pro Glu Phe Ser Gly Ser Arg Val
    450                 455                 460
Ser Leu Thr Asp Ile Pro Thr Glu Asp Glu Ala Leu Gly Thr Pro Glu
465                 470                 475                 480
Thr Gly Ala Ala Thr Pro Met Asp Trp Gln Glu Gln Gly Arg Ala Pro
                485                 490                 495
Ser Gln Asp Gln Glu Ala Pro Ser Pro Glu Ala Leu Pro Ser Pro Gly
            500                 505                 510
Gln Glu Pro Ala Ala Gly Ala Ser Pro Arg Arg Gly Glu Leu Arg Arg
        515                 520                 525
Gly Ser Ser Ala Glu Ser Ala Leu Pro Arg Ala Gly Pro Arg Glu Leu
    530                 535                 540
Gly Arg Gly Leu His Lys Ala Ala Ser Val Glu Leu Pro Gln Arg Arg
545                 550                 555                 560
Ser Pro Gly Pro Gly Ala Thr Arg Leu Ala Arg Gly Gly Leu Gly Glu
                565                 570                 575
Gly Glu Tyr Ala Gln Arg Leu Gln Ala Leu Arg Gln Arg Leu Leu Arg
            580                 585                 590
Gly Gly Pro Glu Asp Gly Lys Val Ser Gly Leu Arg Gly Pro Leu Leu
        595                 600                 605
Glu Ser Leu Gly Gly Arg Ala Arg Asp Pro Arg Met Ala Arg Ala Ala
    610                 615                 620
Ser Ser Glu Ala Ala Pro His His Gln Pro Pro Leu Glu Asn Arg Gly
625                 630                 635                 640
Leu Gln Lys Ser Ser Ser Phe Ser Gln Gly Glu Ala Glu Pro Arg Gly
                645                 650                 655
Arg His Arg Arg Ala Gly Ala Pro Leu Glu Ile Pro Val Ala Arg Leu
            660                 665                 670
Gly Ala Arg Arg Leu Gln Glu Ser Pro Ser Leu Ser Ala Leu Ser Glu
        675                 680                 685
Ala Gln Pro Ser Ser Pro Ala Arg Pro Ser Ala Pro Lys Pro Ser Thr
    690                 695                 700
Pro Lys Ser Ala Glu Pro Ser Ala Thr Thr Pro Ser Asp Ala Pro Gln
705                 710                 715                 720
Pro Pro Ala Pro Gln Pro Ala Gln Asp Lys Ala Pro Glu Pro Arg Pro
                725                 730                 735
Glu Pro Val Arg Ala Ser Lys Pro Ala Pro Pro Pro Gln Ala Leu Gln
            740                 745                 750
Thr Leu Ala Leu Pro Leu Thr Pro Tyr Ala Gln Ile Ile Gln Ser Leu
        755                 760                 765
Gln Leu Ser Gly His Ala Gln Gly Pro Ser Gln Gly Pro Ala Ala Pro
    770                 775                 780
Pro Ser Glu Pro Lys Pro His Ala Ala Val Phe Ala Arg Val Ala Ser
785                 790                 795                 800
Pro Pro Pro Gly Ala Pro Glu Lys Arg Val Pro Ser Ala Gly Gly Pro
                805                 810                 815
Pro Val Leu Ala Glu Lys Ala Arg Val Pro Thr Val Pro Pro Arg Pro
            820                 825                 830
Gly Ser Ser Leu Ser Ser Ser Ile Glu Asn Leu Glu Ser Glu
        835                 840                 845
```

<210> 5
<211> 279
<212> PRT
<213> Human

<400> 5
Ser Pro Ala Lys Glu Val Val Ser Ser Pro Gly Ser Ser Pro Arg Ser
1 5 10 15
Ser Pro Arg Pro Glu Gly Thr Thr Leu Arg Gln Gly Pro Pro Gln Lys
20 25 30
Pro Tyr Thr Phe Leu Glu Glu Lys Ala Arg Gly Arg Phe Gly Val Val
35 40 45
Arg Ala Cys Arg Glu Asn Ala Thr Gly Arg Thr Phe Val Ala Lys Ile
50 55 60
Val Pro Tyr Ala Ala Glu Gly Lys Pro Arg Val Leu Gln Glu Tyr Glu
65 70 75 80
Val Leu Arg Thr Leu His His Glu Arg Ile Met Ser Leu His Glu Ala
85 90 95
Tyr Ile Thr Pro Arg Tyr Leu Val Leu Ile Ala Glu Ser Cys Gly Asn
100 105 110
Arg Glu Leu Leu Cys Gly Leu Ser Asp Arg Phe Arg Tyr Ser Glu Asp
115 120 125
Asp Val Ala Thr Tyr Met Val Gln Leu Leu Gln Gly Leu Asp Tyr Leu
130 135 140
His Gly His His Val Leu His Leu Asp Ile Lys Pro Asp Asn Leu Leu
145 150 155 160
Leu Ala Pro Asp Asn Ala Leu Lys Ile Val Asp Phe Gly Ser Ala Gln
165 170 175
Pro Tyr Asn Pro Gln Ala Leu Arg Pro Leu Gly His Arg Thr Gly Thr
180 185 190
Leu Glu Phe Met Ala Pro Glu Met Val Lys Gly Glu Pro Ile Gly Ser
195 200 205
Ala Thr Asp Ile Trp Gly Ala Gly Val Leu Thr Tyr Ile Met Leu Ser
210 215 220
Gly Arg Ser Pro Phe Tyr Glu Pro Asp Pro Gln Glu Thr Glu Ala Arg
225 230 235 240
Ile Val Gly Gly Arg Phe Asp Ala Phe Gln Leu Tyr Pro Asn Thr Ser
245 250 255
Gln Ser Ala Thr Leu Phe Leu Arg Lys Val Leu Ser Val His Pro Trp
260 265 270
Ser Arg Pro Ser Ser Cys Leu
275

<210> 6
<211> 549
<212> PRT
<213> Human

<400> 6
Leu Arg Glu Pro Gly Trp Ala Ala Thr Gly Leu Arg Lys Gly Val Gln
1 5 10 15
His Ile Phe Arg Val Leu Ser Thr Thr Val Lys Ser Ser Ser Lys Pro
20 25 30
Ser Pro Pro Ser Glu Pro Val Gln Leu Leu Glu His Gly Pro Thr Leu
35 40 45
Glu Glu Ala Pro Ala Met Leu Asp Lys Pro Asp Ile Val Tyr Val Val
50 55 60
Glu Gly Gln Pro Ala Ser Val Thr Val Thr Phe Asn His Val Glu Ala
65 70 75 80
Gln Val Val Trp Arg Ser Cys Arg Gly Ala Leu Leu Glu Ala Arg Ala

```
                85                  90                  95
Gly Val Tyr Glu Leu Ser Gln Pro Asp Asp Asp Gln Tyr Cys Leu Arg
            100                 105                 110
Ile Cys Arg Val Ser Arg Arg Asp Met Gly Ala Leu Thr Cys Thr Ala
        115                 120                 125
Arg Asn Arg His Gly Thr Gln Thr Cys Ser Val Thr Leu Glu Leu Ala
    130                 135                 140
Glu Ala Pro Arg Phe Glu Ser Ile Met Glu Asp Val Glu Val Gly Ala
145                 150                 155                 160
Gly Glu Thr Ala Arg Phe Ala Val Val Val Glu Gly Lys Pro Leu Pro
                165                 170                 175
Asp Ile Met Trp Tyr Lys Asp Glu Val Leu Leu Thr Glu Ser Ser His
            180                 185                 190
Val Ser Phe Val Tyr Glu Glu Asn Glu Cys Ser Leu Val Val Leu Ser
        195                 200                 205
Thr Gly Ala Gln Asp Gly Gly Val Tyr Thr Cys Thr Ala Gln Asn Leu
    210                 215                 220
Ala Gly Glu Val Ser Cys Lys Ala Glu Leu Ala Val His Ser Ala Gln
225                 230                 235                 240
Thr Ala Met Glu Val Glu Gly Val Gly Glu Asp Glu Asp His Arg Gly
                245                 250                 255
Arg Arg Leu Ser Asp Phe Tyr Asp Ile His Gln Glu Ile Gly Arg Gly
            260                 265                 270
Ala Phe Ser Tyr Leu Arg Arg Ile Val Glu Arg Ser Ser Gly Leu Glu
        275                 280                 285
Phe Ala Ala Lys Phe Ile Pro Ser Gln Ala Lys Pro Lys Ala Ser Ala
    290                 295                 300
Arg Arg Glu Ala Arg Leu Leu Ala Arg Leu Gln His Asp Cys Val Leu
305                 310                 315                 320
Tyr Phe His Glu Ala Phe Glu Arg Arg Arg Gly Leu Val Ile Val Thr
                325                 330                 335
Glu Leu Cys Thr Glu Glu Leu Leu Glu Arg Ile Ala Arg Lys Pro Thr
            340                 345                 350
Val Cys Glu Ser Glu Ile Arg Ala Tyr Met Arg Gln Val Leu Glu Gly
        355                 360                 365
Ile His Tyr Leu His Gln Ser His Val Leu His Leu Asp Val Lys Pro
    370                 375                 380
Glu Asn Leu Leu Val Trp Asp Gly Ala Ala Gly Glu Gln Gln Val Arg
385                 390                 395                 400
Ile Cys Asp Phe Gly Asn Ala Gln Glu Leu Thr Pro Gly Glu Pro Gln
                405                 410                 415
Tyr Cys Gln Tyr Gly Thr Pro Glu Phe Val Ala Pro Glu Ile Val Asn
            420                 425                 430
Gln Ser Pro Val Ser Gly Val Thr Asp Ile Trp Pro Val Gly Val Val
        435                 440                 445
Ala Phe Leu Cys Leu Thr Gly Ile Ser Pro Phe Val Gly Glu Asn Asp
    450                 455                 460
Arg Thr Thr Leu Met Asn Ile Arg Asn Tyr Asn Val Ala Phe Glu Glu
465                 470                 475                 480
Thr Thr Phe Leu Ser Leu Ser Arg Glu Ala Arg Gly Phe Leu Ile Lys
                485                 490                 495
Val Leu Val Gln Asp Arg Leu Arg Pro Thr Ala Glu Glu Thr Leu Glu
            500                 505                 510
His Pro Trp Phe Lys Thr Gln Ala Lys Gly Ala Glu Val Ser Thr Asp
        515                 520                 525
His Leu Lys Leu Phe Leu Ser Arg Arg Arg Trp Gln Arg Ser Gln Ile
    530                 535                 540
Ser Tyr Lys Cys His
545
```

<210> 7
<211> 250
<212> PRT
<213> Human

<400> 7
Tyr Thr Phe Leu Glu Glu Lys Ala Arg Gly Arg Phe Gly Val Val Arg
 1   5   10   15
Ala Cys Arg Glu Asn Ala Thr Gly Arg Thr Phe Val Ala Lys Ile Val
            20   25   30
Pro Tyr Ala Ala Glu Gly Lys Pro Arg Val Leu Gln Glu Tyr Glu Val
        35   40   45
Leu Arg Thr Leu His His Glu Arg Ile Met Ser Leu His Glu Ala Tyr
    50   55   60
Ile Thr Pro Arg Tyr Leu Val Leu Ile Ala Glu Ser Cys Gly Asn Arg
65   70   75   80
Glu Leu Leu Cys Gly Leu Ser Asp Arg Phe Arg Tyr Ser Glu Asp Asp
                85   90   95
Val Ala Thr Tyr Met Val Gln Leu Leu Gln Gly Leu Asp Tyr Leu His
            100   105   110
Gly His His Val Leu His Leu Asp Ile Lys Pro Asp Asn Leu Leu Leu
        115   120   125
Ala Pro Asp Asn Ala Leu Lys Ile Val Asp Phe Gly Ser Ala Gln Pro
    130   135   140
Tyr Asn Pro Gln Ala Leu Arg Pro Leu Gly His Arg Thr Gly Thr Leu
145   150   155   160
Glu Phe Met Ala Pro Glu Met Val Lys Gly Glu Pro Ile Gly Ser Ala
                165   170   175
Thr Asp Ile Trp Gly Ala Gly Val Leu Thr Tyr Ile Met Leu Ser Gly
            180   185   190
Arg Ser Pro Phe Tyr Glu Pro Asp Pro Gln Glu Thr Glu Ala Arg Ile
        195   200   205
Val Gly Gly Arg Phe Asp Ala Phe Gln Leu Tyr Pro Asn Thr Ser Gln
    210   215   220
Ser Ala Thr Leu Phe Leu Arg Lys Val Leu Ser Val His Pro Trp Ser
225   230   235   240
Arg Pro Ser Ser Cys Leu Ser Val Cys His
                245   250

<210> 8
<211> 245
<212> PRT
<213> Human

<400> 8
Pro Arg Lys Asp Lys Gly Leu Ser Pro Pro Asn Leu Ser Ala Ser Val
 1   5   10   15
Gln Glu Glu Leu Gly His Gln Tyr Val Arg Ser Glu Ser Asp Phe Pro
            20   25   30
Pro Val Phe His Ile Lys Leu Lys Asp Gln Val Leu Leu Glu Gly Glu
        35   40   45
Ala Ala Thr Leu Leu Cys Leu Pro Ala Ala Cys Pro Ala Pro His Ile
    50   55   60
Ser Trp Met Lys Asp Lys Lys Ser Leu Arg Ser Glu Pro Ser Val Ile
65   70   75   80
Ile Val Ser Cys Lys Asp Gly Arg Gln Leu Leu Ser Ile Pro Arg Ala
                85   90   95
Gly Lys Arg His Ala Gly Leu Tyr Glu Cys Ser Ala Thr Asn Val Leu
            100   105   110
Gly Ser Ile Thr Ser Ser Cys Thr Val Ala Val Ala Arg Val Pro Gly

```
        115                 120                 125
Lys Leu Ala Pro Pro Glu Val Thr Gln Thr Tyr Gln Asp Thr Ala Leu
    130                 135                 140
Val Leu Trp Lys Pro Gly Asp Ser Arg Ala Pro Cys Thr Tyr Thr Leu
145                 150                 155                 160
Glu Arg Arg Val Asp Gly Glu Ser Val Trp His Pro Val Ser Ser Gly
                165                 170                 175
Ile Pro Asp Cys Tyr Tyr Asn Val Thr His Leu Pro Val Gly Val Thr
            180                 185                 190
Val Arg Phe Arg Val Ala Cys Ala Asn Arg Ala Gly Gln Gly Pro Phe
        195                 200                 205
Ser Asn Ser Ser Glu Lys Val Phe Val Arg Gly Thr Gln Asp Ser Ser
    210                 215                 220
Ala Val Pro Ser Ala Ala His Gln Glu Ala Pro Val Thr Ser Arg Pro
225                 230                 235                 240
Ala Arg Ala Arg Pro
                245
```

<210> 9
<211> 111
<212> PRT
<213> Human

<400> 9

```
Leu Glu Asp Val Glu Val Leu Glu Gly Arg Ala Ala Arg Phe Asp Cys
 1               5                  10                  15
Lys Ile Ser Gly Thr Pro Pro Pro Val Val Thr Trp Thr His Phe Gly
            20                  25                  30
Cys Pro Met Glu Glu Ser Glu Asn Leu Arg Leu Arg Gln Asp Gly Gly
        35                  40                  45
Leu His Ser Leu His Ile Ala His Val Gly Ser Glu Asp Glu Gly Leu
    50                  55                  60
Tyr Ala Val Ser Ala Val Asn Thr His Gly Gln Ala His Cys Ser Ala
65                  70                  75                  80
Gln Leu Tyr Val Glu Glu Pro Arg Thr Ala Ala Ser Gly Pro Ser Ser
                85                  90                  95
Lys Leu Glu Lys Met Pro Ser Ile Pro Glu Glu Pro Glu Gln Gly
            100                 105                 110
```

<210> 10
<211> 198
<212> PRT
<213> Human

<400> 10

```
Pro Asp Phe Leu Arg Pro Leu Gln Asp Leu Glu Val Gly Leu Ala Lys
 1               5                  10                  15
Glu Ala Met Leu Glu Cys Gln Val Thr Gly Leu Pro Tyr Pro Thr Ile
            20                  25                  30
Ser Trp Phe His Asn Gly His Arg Ile Gln Ser Ser Asp Asp Arg Arg
        35                  40                  45
Met Thr Gln Tyr Arg Asp Val His Arg Leu Val Phe Pro Ala Val Gly
    50                  55                  60
Pro Gln His Ala Gly Val Tyr Lys Ser Val Ile Ala Asn Lys Leu Gly
65                  70                  75                  80
Lys Ala Ala Cys Tyr Ala His Leu Tyr Val Thr Asp Val Val Pro Gly
                85                  90                  95
Pro Pro Asp Gly Ala Pro Gln Val Val Ala Val Thr Gly Arg Met Val
            100                 105                 110
```

```
Thr Leu Thr Trp Asn Pro Pro Arg Ser Leu Asp Met Ala Ile Asp Pro
        115                 120                 125
Asp Ser Leu Thr Tyr Thr Val Gln His Gln Val Leu Gly Ser Asp Gln
    130                 135                 140
Trp Thr Ala Leu Val Thr Gly Leu Arg Glu Pro Gly Trp Ala Ala Thr
145                 150                 155                 160
Gly Leu Arg Lys Gly Val Gln His Ile Phe Arg Val Leu Ser Thr Thr
                165                 170                 175
Val Lys Ser Ser Ser Lys Pro Ser Pro Pro Ser Glu Pro Val Gln Leu
            180                 185                 190
Leu Glu His Gly Pro Thr
        195
```

<210> 11
<211> 101
<212> PRT
<213> Human

<400> 11

```
Ala Pro Leu Phe Thr Arg Leu Leu Glu Asp Val Glu Val Leu Glu Gly
 1               5                  10                  15
Arg Ala Ala Arg Phe Asp Cys Lys Ile Ser Gly Thr Pro Pro Pro Val
            20                  25                  30
Val Thr Trp Thr His Phe Gly Cys Pro Met Glu Glu Ser Glu Asn Leu
        35                  40                  45
Arg Leu Arg Gln Asp Gly Gly Leu His Ser Leu His Ile Ala His Val
    50                  55                  60
Gly Ser Glu Asp Glu Gly Leu Tyr Ala Val Ser Ala Val Asn Thr His
65                  70                  75                  80
Gly Gln Ala His Cys Ser Ala Gln Leu Tyr Val Glu Glu Pro Arg Thr
                85                  90                  95
Ala Ala Ser Gly Pro
            100
```

<210> 12
<211> 195
<212> PRT
<213> Human

<400> 12

```
Arg Gly Thr Gln Asp Ser Ser Ala Val Pro Ser Ala Ala His Gln Glu
 1               5                  10                  15
Ala Pro Val Thr Ser Arg Pro Ala Arg Ala Arg Pro Pro Asp Ser Pro
            20                  25                  30
Thr Ser Leu Ala Pro Pro Leu Ala Pro Ala Ala Pro Thr Pro Pro Ser
        35                  40                  45
Val Thr Val Ser Pro Ser Ser Pro Pro Thr Pro Pro Ser Gln Ala Leu
    50                  55                  60
Ser Ser Leu Lys Ala Val Gly Pro Pro Pro Gln Thr Pro Pro Arg Arg
65                  70                  75                  80
His Arg Gly Leu Gln Ala Ala Arg Pro Ala Glu Pro Thr Leu Pro Ser
                85                  90                  95
Thr His Val Thr Pro Ser Glu Pro Lys Pro Phe Val Leu Asp Thr Gly
            100                 105                 110
Thr Pro Ile Pro Ala Ser Thr Pro Gln Gly Val Lys Pro Val Ser Ser
        115                 120                 125
Ser Thr Pro Val Tyr Val Val Thr Ser Phe Val Ser Ala Pro Pro Ala
    130                 135                 140
Pro Glu Pro Pro Ala Pro Glu Pro Pro Pro Glu Pro Thr Lys Val Thr
```

```
145                 150                 155                 160
Val Gln Ser Leu Ser Pro Ala Lys Glu Val Val Ser Ser Pro Gly Ser
                165                 170                 175
Ser Pro Arg Ser Ser Pro Arg Pro Glu Gly Thr Thr Leu Arg Gln Gly
            180                 185                 190
Pro Pro Gln
        195
```

<210> 13
<211> 90
<212> PRT
<213> Human

<400> 13

```
Pro Asp Phe Leu Arg Pro Leu Gln Asp Leu Glu Val Gly Leu Ala Lys
 1               5                  10                  15
Glu Ala Met Leu Glu Cys Gln Val Thr Gly Leu Pro Tyr Pro Thr Ile
            20                  25                  30
Ser Trp Phe His Asn Gly His Arg Ile Gln Ser Ser Asp Asp Arg Arg
        35                  40                  45
Met Thr Gln Tyr Arg Asp Val His Arg Leu Val Phe Pro Ala Val Gly
    50                  55                  60
Pro Gln His Ala Gly Val Tyr Lys Ser Val Ile Ala Asn Lys Leu Gly
65                  70                  75                  80
Lys Ala Ala Cys Tyr Ala His Leu Tyr Val
                85                  90
```

<210> 14
<211> 414
<212> PRT
<213> Human

<400> 14

```
Pro Pro Glu Phe Val Ile Pro Leu Ser Glu Val Thr Cys Glu Thr Gly
 1               5                  10                  15
Glu Thr Val Val Leu Arg Cys Arg Val Cys Gly Arg Pro Lys Ala Ser
            20                  25                  30
Ile Thr Trp Lys Gly Pro Glu His Asn Thr Leu Asn Asn Asp Gly His
        35                  40                  45
Tyr Ser Ile Ser Tyr Ser Asp Leu Gly Glu Ala Thr Leu Lys Ile Val
    50                  55                  60
Gly Val Thr Thr Glu Asp Asp Gly Ile Tyr Thr Cys Ile Ala Val Asn
65                  70                  75                  80
Asp Met Gly Ser Ala Ser Ser Ser Ala Ser Leu Arg Val Leu Gly Pro
                85                  90                  95
Gly Met Asp Gly Ile Met Val Thr Trp Lys Asp Asn Phe Asp Ser Phe
            100                 105                 110
Tyr Ser Glu Val Ala Glu Leu Gly Arg Gly Arg Phe Ser Val Val Lys
        115                 120                 125
Lys Cys Asp Gln Lys Gly Thr Lys Arg Ala Val Ala Thr Lys Phe Val
    130                 135                 140
Asn Lys Lys Leu Met Lys Arg Asp Gln Val Thr His Glu Leu Gly Ile
145                 150                 155                 160
Leu Gln Ser Leu Gln His Pro Leu Leu Val Gly Leu Leu Asp Thr Phe
                165                 170                 175
Glu Thr Pro Thr Ser Tyr Ile Leu Val Leu Glu Met Ala Asp Gln Gly
            180                 185                 190
Arg Leu Leu Asp Cys Val Val Arg Trp Gly Ser Leu Thr Glu Gly Lys
        195                 200                 205
```

```
Ile Arg Ala His Leu Gly Glu Val Leu Glu Ala Val Arg Tyr Leu His
    210                 215                 220
Asn Cys Arg Ile Ala His Leu Asp Leu Lys Pro Glu Asn Ile Leu Val
225                 230                 235                 240
Asp Glu Ser Leu Ala Lys Pro Thr Ile Lys Leu Ala Asp Phe Gly Asp
                245                 250                 255
Ala Val Gln Leu Asn Thr Thr Tyr Tyr Ile His Gln Leu Leu Gly Asn
            260                 265                 270
Pro Glu Phe Ala Ala Pro Glu Ile Ile Leu Gly Asn Pro Val Ser Leu
        275                 280                 285
Thr Ser Asp Thr Trp Ser Val Gly Val Leu Thr Tyr Val Leu Leu Ser
    290                 295                 300
Gly Val Ser Pro Phe Leu Asp Asp Ser Val Glu Glu Thr Cys Leu Asn
305                 310                 315                 320
Ile Cys Arg Leu Asp Phe Ser Phe Pro Asp Asp Tyr Phe Lys Gly Val
                325                 330                 335
Ser Gln Lys Ala Lys Glu Phe Val Cys Phe Leu Leu Gln Glu Asp Pro
            340                 345                 350
Ala Lys Arg Pro Ser Ala Ala Leu Ala Leu Gln Glu Gln Trp Leu Gln
        355                 360                 365
Ala Gly Asn Gly Arg Ser Thr Gly Val Leu Asp Thr Ser Arg Leu Thr
    370                 375                 380
Ser Phe Ile Glu Arg Arg Lys His Gln Asn Asp Val Arg Pro Ile Arg
385                 390                 395                 400
Ser Ile Lys Asn Phe Leu Gln Ser Arg Leu Leu Pro Arg Val
                405                 410
```

<210> 15
<211> 274
<212> PRT
<213> Human

<400> 15

```
Glu Leu Gly Arg Gly Arg Phe Ser Val Val Lys Lys Cys Asp Gln Lys
 1               5                  10                  15
Gly Thr Lys Arg Ala Val Ala Thr Lys Phe Val Asn Lys Lys Leu Met
            20                  25                  30
Lys Arg Asp Gln Val Thr His Glu Leu Gly Ile Leu Gln Ser Leu Gln
        35                  40                  45
His Pro Leu Leu Val Gly Leu Leu Asp Thr Phe Glu Thr Pro Thr Ser
    50                  55                  60
Tyr Ile Leu Val Leu Glu Met Ala Asp Gln Gly Arg Leu Leu Asp Cys
65                  70                  75                  80
Val Val Arg Trp Gly Ser Leu Thr Glu Gly Lys Ile Arg Ala His Leu
                85                  90                  95
Gly Glu Val Leu Glu Ala Val Arg Tyr Leu His Asn Cys Arg Ile Ala
            100                 105                 110
His Leu Asp Leu Lys Pro Glu Asn Ile Leu Val Asp Glu Ser Leu Ala
        115                 120                 125
Lys Pro Thr Ile Lys Leu Ala Asp Phe Gly Asp Ala Val Gln Leu Asn
    130                 135                 140
Thr Thr Tyr Tyr Ile His Gln Leu Leu Gly Asn Pro Glu Phe Ala Ala
145                 150                 155                 160
Pro Glu Ile Ile Leu Gly Asn Pro Val Ser Leu Thr Ser Asp Thr Trp
                165                 170                 175
Ser Val Gly Val Leu Thr Tyr Val Leu Leu Ser Gly Val Ser Pro Phe
            180                 185                 190
Leu Asp Asp Ser Val Glu Glu Thr Cys Leu Asn Ile Cys Arg Leu Asp
        195                 200                 205
Phe Ser Phe Pro Asp Asp Tyr Phe Lys Gly Val Ser Gln Lys Ala Lys
```

```
    210                 215                 220
Glu Phe Val Cys Phe Leu Leu Gln Glu Asp Pro Ala Lys Arg Pro Ser
225                 230                 235                 240
Ala Ala Leu Ala Leu Gln Glu Gln Trp Leu Gln Ala Gly Asn Gly Arg
                245                 250                 255
Ser Thr Gly Val Leu Asp Thr Ser Arg Leu Thr Ser Phe Ile Glu Arg
            260                 265                 270
Arg Lys
```

<210> 16
<211> 141
<212> PRT
<213> Human

<400> 16

```
Gly Lys Arg Glu Gly Lys Leu Glu Asn Gly Tyr Arg Lys Ser Arg Glu
 1               5                  10                  15
Gly Leu Ser Asn Lys Val Ser Val Lys Leu Leu Asn Pro Asn Tyr Ile
            20                  25                  30
Tyr Asp Val Pro Pro Glu Phe Val Ile Pro Leu Ser Glu Val Thr Cys
        35                  40                  45
Glu Thr Gly Glu Thr Val Val Leu Arg Cys Arg Val Cys Gly Arg Pro
    50                  55                  60
Lys Ala Ser Ile Thr Trp Lys Gly Pro Glu His Asn Thr Leu Asn Asn
65                  70                  75                  80
Asp Gly His Tyr Ser Ile Ser Tyr Ser Asp Leu Gly Glu Ala Thr Leu
                85                  90                  95
Lys Ile Val Gly Val Thr Thr Glu Asp Asp Gly Ile Tyr Thr Cys Ile
            100                 105                 110
Ala Val Asn Asp Met Gly Ser Ala Ser Ser Ser Ala Ser Leu Arg Val
        115                 120                 125
Leu Gly Pro Gly Met Asp Gly Ile Met Val Thr Trp Lys
    130                 135                 140
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<210> 17
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<213> Human

<400> 17

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Cys Gly Gly Ala Pro Ser Thr Ser Arg Ser Arg Pro Ser Arg Ile Pro
            20                  25                  30
Gln Pro Val Arg His His Pro Pro Val Leu Val Ser Ser Ala Ala Ser
        35                  40                  45
Ser Gln Ala Glu Ala Asp Lys Met Ser Gly Thr Ser Thr Pro Gly Pro
    50                  55                  60
Ser Leu Pro Pro Pro Gly Ala Ala Pro Glu Ala Gly Pro Ser Ala Pro
65                  70                  75                  80
Ser Arg Arg Pro Pro Gly Ala Asp Ala Glu Gly Ser Glu Arg Glu Ala
                85                  90                  95
Glu Pro Ile Pro Lys Met Lys Val Leu Glu Ser Pro Arg Lys Gly Ala
            100                 105                 110
Ala Asn Ala Ser Gly Ser Ser Pro Asp Ala Pro Ala Lys Asp Ala Arg
        115                 120                 125
Ala Ser Leu Gly Thr Leu Pro Leu Gly Lys Pro Arg Ala Gly Ala Ala
    130                 135                 140
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```
Ser Pro Leu Asn Ser Pro Leu Ser Ser Ala Val Pro Ser Leu Gly Lys
145                 150                 155                 160
Glu Pro Phe Pro Pro Ser Ser Pro Leu Gln Lys Gly Gly Ser Phe Trp
                165                 170                 175
Ser Ser Ile Pro Ala Ser Pro Ala Ser Arg Pro Gly Ser Phe Thr Phe
            180                 185                 190
Pro Gly Asp Ser
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<210> 18
<211> 298
<212> PRT
<213> Human

<400> 18

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Lys Phe Gly Gln Val Phe Arg Leu Val Glu Lys Lys Thr Arg Lys Val
            20                  25                  30
Trp Ala Gly Lys Phe Phe Lys Ala Tyr Ser Ala Lys Glu Lys Glu Asn
        35                  40                  45
Ile Arg Gln Glu Ile Ser Ile Met Asn Cys Leu His His Pro Lys Leu
    50                  55                  60
Val Gln Cys Val Asp Ala Phe Glu Glu Lys Ala Asn Ile Val Met Val
65                  70                  75                  80
Leu Glu Ile Val Ser Gly Gly Glu Leu Phe Glu Arg Ile Ile Asp Glu
                85                  90                  95
Asp Phe Glu Leu Thr Glu Arg Glu Cys Ile Lys Tyr Met Arg Gln Ile
            100                 105                 110
Ser Glu Gly Val Glu Tyr Ile His Lys Gln Gly Ile Val His Leu Asp
        115                 120                 125
Leu Lys Pro Glu Asn Ile Met Cys Val Asn Lys Thr Gly Thr Arg Ile
    130                 135                 140
Lys Leu Ile Asp Phe Gly Leu Ala Arg Arg Leu Glu Asn Ala Gly Ser
145                 150                 155                 160
Leu Lys Val Leu Phe Gly Thr Pro Glu Phe Val Ala Pro Glu Val Ile
                165                 170                 175
Asn Tyr Glu Pro Ile Ser Tyr Ala Thr Asp Met Trp Ser Ile Gly Val
            180                 185                 190
Ile Cys Tyr Ile Leu Val Ser Gly Leu Ser Pro Phe Met Gly Asp Asn
        195                 200                 205
Asp Asn Glu Thr Leu Ala Asn Val Thr Ser Ala Thr Trp Asp Phe Asp
    210                 215                 220
Asp Glu Ala Phe Asp Glu Ile Ser Asp Asp Ala Lys Asp Phe Ile Ser
225                 230                 235                 240
Asn Leu Leu Lys Lys Asp Met Lys Asn Arg Leu Asp Cys Thr Gln Cys
                245                 250                 255
Leu Gln His Pro Trp Leu Met Lys Asp Thr Lys Asn Met Glu Ala Lys
            260                 265                 270
Lys Leu Ser Lys Asp Arg Met Lys Lys Tyr Met Ala Arg Arg Lys Trp
        275                 280                 285
Gln Lys Thr Gly Asn Ala Val Arg Ala Ile
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<211> 508
<212> PRT
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<400> 19

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Pro Pro Lys Ala Ala Met Pro Pro Gln Ile Ile Gln Phe Pro Glu Asp
            20                  25                  30
Gln Lys Val Arg Ala Gly Glu Ser Val Glu Leu Phe Gly Lys Val Thr
        35                  40                  45
Gly Thr Gln Pro Ile Thr Cys Thr Trp Met Lys Phe Arg Lys Gln Ile
    50                  55                  60
Gln Asp Ser Glu His Ile Lys Val Glu Asn Ser Glu Asn Gly Ser Lys
65                  70                  75                  80
Leu Thr Ile Leu Ala Ala Arg Gln Glu His Cys Gly Cys Tyr Thr Leu
                85                  90                  95
Leu Val Glu Asn Lys Leu Gly Ser Arg Gln Ala Gln Val Asn Leu Thr
            100                 105                 110
Val Val Asp Lys Pro Asp Pro Pro Ala Gly Thr Pro Cys Ala Ser Asp
        115                 120                 125
Ile Arg Ser Ser Ser Leu Thr Leu Ser Trp Tyr Gly Ser Ser Tyr Asp
    130                 135                 140
Gly Gly Ser Ala Val Gln Ser Tyr Ser Ile Glu Ile Trp Asp Ser Ala
145                 150                 155                 160
Asn Lys Thr Trp Lys Glu Leu Ala Thr Cys Arg Ser Thr Ser Phe Asn
                165                 170                 175
Val Gln Asp Leu Leu Pro Asp His Glu Tyr Lys Phe Arg Val Arg Ala
            180                 185                 190
Ile Asn Val Tyr Gly Thr Ser Glu Pro Ser Gln Glu Ser Glu Leu Thr
        195                 200                 205
Thr Val Gly Glu Lys Pro Glu Glu Pro Lys Met Lys Trp Arg Cys Gln
    210                 215                 220
Thr Asp Asp Glu Lys Glu Pro Glu Val Asp Tyr Arg Thr Val Thr Ile
225                 230                 235                 240
Asn Thr Glu Gln Lys Val Ser Asp Phe Tyr Asp Ile Glu Glu Arg Leu
                245                 250                 255
Gly Ser Gly Lys Phe Gly Gln Val Phe Arg Leu Val Glu Lys Lys Thr
            260                 265                 270
Arg Lys Val Trp Ala Gly Lys Phe Phe Lys Ala Tyr Ser Ala Lys Glu
        275                 280                 285
Lys Glu Asn Ile Arg Gln Glu Ile Ser Ile Met Asn Cys Leu His His
    290                 295                 300
Pro Lys Leu Val Gln Cys Val Asp Ala Phe Glu Glu Lys Ala Asn Ile
305                 310                 315                 320
Val Met Val Leu Glu Ile Val Ser Gly Gly Glu Leu Phe Glu Arg Ile
                325                 330                 335
Ile Asp Glu Asp Phe Glu Leu Thr Glu Arg Glu Cys Ile Lys Tyr Met
            340                 345                 350
Arg Gln Ile Ser Glu Gly Val Glu Tyr Ile His Lys Gln Gly Ile Val
        355                 360                 365
His Leu Asp Leu Lys Pro Glu Asn Ile Met Cys Val Asn Lys Thr Gly
    370                 375                 380
Thr Arg Ile Lys Leu Ile Asp Phe Gly Leu Ala Arg Arg Leu Glu Asn
385                 390                 395                 400
Ala Gly Ser Leu Lys Val Leu Phe Gly Thr Pro Glu Phe Val Ala Pro
                405                 410                 415
Glu Val Ile Asn Tyr Glu Pro Ile Ser Tyr Ala Thr Asp Met Trp Ser
            420                 425                 430
Ile Gly Val Ile Cys Tyr Ile Leu Val Ser Gly Leu Ser Pro Phe Met
        435                 440                 445
Gly Asp Asn Asp Asn Glu Thr Leu Ala Asn Val Thr Ser Ala Thr Trp
    450                 455                 460
Asp Phe Asp Asp Glu Ala Phe Asp Glu Ile Ser Asp Asp Ala Lys Asp
465                 470                 475                 480
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Phe Ile Ser Asn Leu Leu Lys Lys Asp Met Lys Asn Arg Leu Asp Cys
                485                 490                 495
Thr Gln Cys Leu Gln His Pro Trp Leu Met Lys Asp
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<211> 106
<212> PRT
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<400> 20

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 1               5                  10                  15
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            20                  25                  30
Val Trp Phe Lys Asp Asp Gln Ser Ile Arg Glu Ser Arg His Phe Gln
        35                  40                  45
Ile Asp Tyr Asp Glu Asp Gly Asn Cys Ser Leu Ile Ile Ser Asp Val
    50                  55                  60
Cys Gly Asp Asp Asp Ala Lys Tyr Thr Cys Lys Ala Val Asn Ser Leu
65                  70                  75                  80
Gly Glu Ala Thr Cys Thr Ala Glu Leu Ile Val Glu Thr Met Glu Glu
                85                  90                  95
Gly Glu Gly Glu Gly Glu Glu Glu Glu Glu
            100                 105
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<210> 21
<211> 96
<212> PRT
<213> Human

<400> 21

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Pro Pro Lys Phe Ala Thr Lys Leu Gly Arg Val Val Val Lys Glu Gly
 1               5                  10                  15
Gln Met Gly Arg Phe Ser Cys Lys Ile Thr Gly Arg Pro Gln Pro Gln
            20                  25                  30
Val Thr Trp Leu Lys Gly Asn Val Pro Leu Gln Pro Ser Ala Arg Val
        35                  40                  45
Ser Val Ser Glu Lys Asn Gly Met Gln Val Leu Glu Ile His Gly Val
    50                  55                  60
Asn Gln Asp Asp Val Gly Val Tyr Thr Cys Leu Val Val Asn Gly Ser
65                  70                  75                  80
Gly Lys Ala Ser Met Ser Ala Glu Leu Ser Ile Gln Gly Leu Asp Ser
                85                  90                  95
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<210> 22
<211> 96
<212> PRT
<213> Human

<400> 22

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Pro Pro Lys Phe Ala Thr Lys Leu Gly Arg Val Val Val Lys Glu Gly
 1               5                  10                  15
Gln Met Gly Arg Phe Ser Cys Lys Ile Thr Gly Arg Pro Gln Pro Gln
            20                  25                  30
Val Thr Trp Leu Lys Gly Asn Val Pro Leu Gln Pro Ser Ala Arg Val
        35                  40                  45
Ser Val Ser Glu Lys Asn Gly Met Gln Val Leu Glu Ile His Gly Val
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    50                  55                  60
Asn Gln Asp Asp Val Gly Val Tyr Thr Cys Leu Val Val Asn Gly Ser
65                  70                  75                  80
Gly Lys Ala Ser Met Ser Ala Glu Leu Ser Ile Gln Gly Leu Asp Ser
                85                  90                  95


<210> 23
<211> 88
<212> PRT
<213> Human

<400> 23
Pro Lys Phe Ala Thr Lys Leu Gly Arg Val Val Val Lys Glu Gly Gln
 1               5                  10                  15
Met Gly Arg Phe Ser Cys Lys Ile Thr Gly Arg Pro Gln Pro Gln Val
            20                  25                  30
Thr Trp Leu Lys Gly Asn Val Pro Leu Gln Pro Ser Ala Arg Val Ser
        35                  40                  45
Val Ser Glu Lys Asn Gly Met Gln Val Leu Glu Ile His Gly Val Asn
    50                  55                  60
Gln Asp Asp Val Gly Val Tyr Thr Cys Leu Val Val Asn Gly Ser Gly
65                  70                  75                  80
Lys Ala Ser Met Ser Ala Glu Leu
                85


<210> 24
<211> 94
<212> PRT
<213> Human

<400> 24
Ala Pro Ser Phe Ser Ser Val Leu Lys Asp Cys Ala Val Ile Glu Gly
 1               5                  10                  15
Gln Asp Phe Val Leu Gln Cys Ser Val Arg Gly Thr Pro Val Pro Arg
            20                  25                  30
Ile Thr Trp Leu Leu Asn Gly Gln Pro Ile Gln Tyr Ala Arg Ser Thr
        35                  40                  45
Cys Glu Ala Gly Val Ala Glu Leu His Ile Gln Asp Ala Leu Pro Glu
    50                  55                  60
Asp His Gly Thr Tyr Thr Cys Leu Ala Glu Asn Ala Leu Gly Gln Val
65                  70                  75                  80
Ser Cys Ser Ala Trp Val Thr Val His Glu Lys Lys Ser Ser
                85                  90


<210> 25
<211> 112
<212> PRT
<213> Human

<400> 25
Lys Lys Ser Ser Arg Lys Ser Glu Tyr Leu Leu Pro Val Ala Pro Ser
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            20                  25                  30
Met Asp Gly Ser Gln Val Thr Met Thr Val Gln Val Ser Gly Asn Pro
        35                  40                  45
Pro Pro Glu Val Ile Trp Leu His Asn Gly Asn Glu Ile Gln Glu Ser
    50                  55                  60
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Glu Asp Phe His Phe Glu Gln Arg Gly Thr Gln His Ser Leu Trp Ile
65                  70                  75                  80
Gln Glu Val Phe Pro Glu Asp Thr Gly Thr Tyr Thr Cys Glu Ala Trp
                85                  90                  95
Asn Ser Ala Gly Glu Val Arg Thr Gln Ala Val Leu Thr Val Gln Glu
            100                 105                 110


<210> 26
<211> 100
<212> PRT
<213> Human

<400> 26
Ser Met Pro Leu Thr Glu Ala Pro Ala Phe Ile Leu Pro Pro Arg Asn
 1               5                  10                  15
Leu Cys Ile Lys Glu Gly Ala Thr Ala Lys Phe Glu Gly Arg Val Arg
            20                  25                  30
Gly Tyr Pro Glu Pro Gln Val Thr Trp His Arg Asn Gly Gln Pro Ile
        35                  40                  45
Thr Ser Gly Gly Arg Phe Leu Leu Asp Cys Gly Ile Arg Gly Thr Phe
    50                  55                  60
Ser Leu Val Ile His Ala Val His Glu Glu Asp Arg Gly Lys Tyr Thr
65                  70                  75                  80
Cys Glu Ala Thr Asn Gly Ser Gly Ala Arg Gln Val Thr Val Glu Leu
                85                  90                  95
Thr Val Glu Gly
            100


<210> 27
<211> 174
<212> PRT
<213> Human

<400> 27
Pro Ser Gly Glu Glu Arg Lys Arg Pro Ala Pro Pro Arg Pro Ala Thr
 1               5                  10                  15
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            20                  25                  30
Ala Ala Asn Arg Arg Ile Pro Met Glu Gly Gln Arg Asp Ser Ala Phe
        35                  40                  45
Pro Lys Phe Glu Ser Lys Pro Gln Ser Gln Glu Val Lys Glu Asn Gln
    50                  55                  60
Thr Val Lys Phe Arg Cys Glu Val Ser Gly Ile Pro Lys Pro Glu Val
65                  70                  75                  80
Ala Trp Phe Leu Glu Gly Thr Pro Val Arg Arg Gln Glu Gly Ser Ile
                85                  90                  95
Glu Val Tyr Glu Asp Ala Gly Ser His Tyr Leu Cys Leu Leu Lys Ala
            100                 105                 110
Arg Thr Arg Asp Ser Gly Thr Tyr Ser Cys Thr Ala Ser Asn Ala Gln
        115                 120                 125
Gly Gln Val Ser Cys Ser Trp Thr Leu Gln Val Glu Arg Leu Ala Val
    130                 135                 140
Met Glu Val Ala Pro Ser Phe Ser Ser Val Leu Lys Asp Cys Ala Val
145                 150                 155                 160
Ile Glu Gly Gln Asp Phe Val Leu Gln Cys Ser Val Arg Gly
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<210> 28
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<211> 97
<212> PRT
<213> Human

<400> 28
Pro Ala Phe Lys Gln Lys Leu Gln Asp Val His Val Ala Glu Gly Lys
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            20   25   30
Ile Trp Thr Leu Asn Gly Lys Thr Leu Lys Thr Thr Lys Phe Ile Ile
        35   40   45
Leu Ser Gln Glu Gly Ser Leu Cys Ser Val Ser Ile Glu Lys Ala Leu
    50   55   60
Leu Glu Asp Arg Gly Leu Tyr Lys Cys Val Ala Lys Asn Asp Ala Gly
65   70   75   80
Gln Ala Glu Cys Ser Cys Gln Val Thr Val Asp Asp Ala Pro Ala Ser
                85   90   95
Glu

<210> 29
<211> 124
<212> PRT
<213> Human

<400> 29
Glu Ser Gln Gly Thr Ala Pro Ala Phe Lys Gln Lys Leu Gln Asp Val
 1   5   10   15
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            20   25   30
Asp Pro Pro Ala Thr Ile Ile Trp Thr Leu Asn Gly Lys Thr Leu Lys
        35   40   45
Thr Thr Lys Phe Ile Ile Leu Ser Gln Glu Gly Ser Leu Cys Ser Val
    50   55   60
Ser Ile Glu Lys Ala Leu Leu Glu Asp Arg Gly Leu Tyr Lys Cys Val
65   70   75   80
Ala Lys Asn Asp Ala Gly Gln Ala Glu Cys Ser Cys Gln Val Thr Val
                85   90   95
Asp Asp Ala Pro Ala Ser Glu Asn Thr Lys Ala Pro Glu Met Lys Ser
            100   105   110
Arg Arg Pro Lys Ser Ser Leu Pro Pro Val Leu Gly
        115   120

<210> 30
<211> 87
<212> PRT
<213> Human

<400> 30
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            20   25   30
Val Thr Trp His Arg Asn Gly Gln Pro Ile Thr Ser Gly Gly Arg Phe
        35   40   45
Leu Leu Asp Cys Gly Ile Arg Gly Thr Phe Ser Leu Val Ile His Ala
    50   55   60
Val His Glu Glu Asp Arg Gly Lys Tyr Thr Cys Glu Ala Thr Asn Gly
65   70   75   80

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<211> 119
<212> PRT
<213> Human

<400> 31
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            20                  25                  30
Asp Cys Ala Val Ile Glu Gly Gln Asp Phe Val Leu Gln Cys Ser Val
        35                  40                  45
Arg Gly Thr Pro Val Pro Arg Ile Thr Trp Leu Leu Asn Gly Gln Pro
    50                  55                  60
Ile Gln Tyr Ala Arg Ser Thr Cys Glu Ala Gly Val Ala Glu Leu His
65                  70                  75                  80
Ile Gln Asp Ala Leu Pro Glu Asp His Gly Thr Tyr Thr Cys Leu Ala
                85                  90                  95
Glu Asn Ala Leu Gly Gln Val Ser Cys Ser Ala Trp Val Thr Val His
            100                 105                 110
Glu Lys Lys Ser Ser Arg Lys
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<210> 32
<211> 98
<212> PRT
<213> Human

<400> 32
Gly Gln Arg Asp Ser Ala Phe Pro Lys Phe Glu Ser Lys Pro Gln Ser
 1               5                  10                  15
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            20                  25                  30
Gly Ile Pro Lys Pro Glu Val Ala Trp Phe Leu Glu Gly Thr Pro Val
        35                  40                  45
Arg Arg Gln Glu Gly Ser Ile Glu Val Tyr Glu Asp Ala Gly Ser His
    50                  55                  60
Tyr Leu Cys Leu Leu Lys Ala Arg Thr Arg Asp Ser Gly Thr Tyr Ser
65                  70                  75                  80
Cys Thr Ala Ser Asn Ala Gln Gly Gln Val Ser Cys Ser Trp Thr Leu
                85                  90                  95
Gln Val


<210> 33
<211> 82
<212> PRT
<213> Human

<400> 33
Val Thr Ala Ser Leu Gly Gln Ser Val Leu Ile Ser Cys Ala Ile Ala
 1               5                  10                  15
Gly Asp Pro Phe Pro Thr Val His Trp Leu Arg Asp Gly Lys Ala Leu
            20                  25                  30
Cys Lys Asp Thr Gly His Phe Glu Val Leu Gln Asn Glu Asp Val Phe
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        35                  40                  45
Thr Leu Val Leu Lys Lys Val Gln Pro Trp His Ala Gly Gln Tyr Glu
    50                  55                  60
Ile Leu Leu Lys Asn Arg Val Gly Glu Cys Ser Cys Gln Val Ser Leu
65                  70                  75                  80
Met Leu
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<210> 34
<211> 89
<212> PRT
<213> Human

<400> 34

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Ala Ala Arg Phe Asp Cys Lys Ile Glu Gly Tyr Pro Asp Pro Glu Val
            20                  25                  30
Val Trp Phe Lys Asp Asp Gln Ser Ile Arg Glu Ser Arg His Phe Gln
        35                  40                  45
Ile Asp Tyr Asp Glu Asp Gly Asn Cys Ser Leu Ile Ile Ser Asp Val
    50                  55                  60
Cys Gly Asp Asp Asp Ala Lys Tyr Thr Cys Lys Ala Val Asn Ser Leu
65                  70                  75                  80
Gly Glu Ala Thr Cys Thr Ala Glu Leu
                85
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(74) Agent: MILLMAN, Robert, A.; Celera Genomics, Chief Intellectual Property Counsel, 45 West Gude Drive C2-4#21, Rockville, MD 20850 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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Published:
— *with international search report*

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17 July 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/040683 A3

(54) Title: ISOLATED HUMAN KINASE PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN KINASE PROTEINS, AND USES THEREOF

(57) Abstract: The present invention provides amino acid sequences of peptides that are encoded by genes within the human genome, the kinase peptides of the present invention. The present invention specifically provides isolated peptide and nucleic acid molecules, methods of identifying orthologs and paralogs of the transporter peptides, and methods of identifying modulators of the kinase peptides.

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/US 01/32616

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/54 C12N9/12 G01N33/573 C12Q1/68 A61K38/45

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12Q A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, SEQUENCE SEARCH, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 911 408 A (JAPAN SCIENCE & TECH CORP) 28 April 1999 (1999-04-28) the whole document	1-16, 19-23
X	GALLAGHER P J ET AL: "MOLECULAR CHARACTERIZATION OF A MAMMALIAN SMOOTH MUSCLE MYOSIN LIGHT CHAIN KINASE" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 266, no. 35, 15 December 1991 (1991-12-15), pages 23936-23944, XP000979557 ISSN: 0021-9258 the whole document	1-16, 19-23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 2002	19/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Keller, Y

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 01/32616

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 17, 18
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 17, 18

Present claims 17, 18 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

nformation on patent family members

International Application No
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